DISEASES OF THE
WARM CLIMATES

DUBOIS • VAN DEN BERGHE

CFTRI-MYSORE
1020
diseases of the

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DISEASES
OF THE
WARM CLIMATES

DISEASES OF THE WARM CLIMATES

Their Clinical Features, Diagnosis and Treatment

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This edition is dedicated to Joseph Bequaert, one of the original collaborators of Rodhain in the Congo, and to Richard P. Strong, whose insatiable curiosity has led him to conduct several Harvard University research expeditions to the Congo, and whose mastery of the subject and personal qualities have endeared him to his Belgian colleagues and friends.

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FOREWORD

MANY of us who have made visits to the Belgian Congo and have admired the work there in tropical medicine will especially welcome this English edition of "Diseases of the Warm Climates." The authors have had long experience in tropical medicine in the Congo and elsewhere and have also been engaged in teaching and research at the Institute of Tropical Medicine in Antwerp. They should be unusually qualified to give us the rich Belgian experience combined with their view of the observations in other parts of the world.

Both of the authors have traveled widely. As a leprologist, Dr. Dubois has visited India and the United States. Dr. van den Berghe has made many trips to the Americas to collect information and lecture. They have now put their heads together to produce a concise and practical book for physicians interested in tropical medicine, with emphasis on the diagnosis and treatment of diseases commonly found in warm climates.

Physicians of temperate climates have been aroused by the recent war to an appreciation of the importance of tropical medicine, but there is danger that they will gradually lose interest unless it is constantly stimulated. They may forget that the increased rapidity and freedom of travel may at any time bring exotic diseases under their care. If this book, then, stimulates the medical profession to keep up its knowledge in the important field of tropical diseases, the authors will have made a real contribution in bringing it forth.

Washington, D. C.

WILBUR A. SAWYER

PREFACE

The present volume is the result of requests from various Belgian and foreign sources for a new work on tropical diseases. Our effort seems justified by the considerable amount of work and discovery recently effected in the field of the diseases in warm climates, and by the obstacles to scientific communication between 1939 and 1945 which have made the dissemination of such new information so difficult until the present time.

Decisive battles of this war took place in the tropics and provoked research and applications to an extent inconceivable under normal circumstances. Although in many cases provided with limited means, specialists in the warm countries of the earth have not remained inactive. Much of their work, however, has been inaccessible, due not only to the state of war, but to the existence of two worlds, unfortunately too much separated in science—the English-speaking world and that one expressing itself in other languages. It seems to us, therefore, that on the Belgian cross-road of languages and thoughts it would be possible to attempt a new organization and synthesis of current knowledge and a presentation of new material. For the sake of utility we have limited our subject and developed it as briefly as possible, consistent with an adequate exposition of the subject.

The object of this book is to provide, in concise form, accurate information concerning the diagnosis and treatment of diseases commonly found in warm climates.

Its aim is to serve as a guide to the physician practicing in the tropics. It is also addressed to the practitioner in temperate climates who is encountering more and more in the ordinary run of his consultations cases of tropical diseases in people who have come home during the incubation period or who are suffering from more or less delayed relapses.

Although it is never easy to confine within definite geographic limits the diseases of the so-called tropical or, better, warm climates, we have largely limited ourselves to those of the tropics or subtropics. We have, however, included certain cosmopolitan affections which attain severe and grave proportions, in the individual and society, only in those climates. Much of the literature on tropical medicine, because protozoans and helminths are such prominent factors in the important diseases of warm climates, takes the form of complete treatises on parasitology, including all cosmopolitan organisms. We have tried to avoid this tendency toward universality and have deliberately disregarded such diseases as brucellosis, leptospirosis, oxyuriasis, teniasis and others in which the incidence and course do not differ perceptibly in the torrid and temperate zones.

The introductory matter consists of three brief chapters dealing with the geographic distribution of tropical diseases, the physiologic and pathologic effects of climate, and, finally, cosmopolitan diseases which play an ever increasing role in the morbidity and mortality in the tropics, especially among the natives. The essentially clinical viewpoint of the book explains why certain subjects have been dealt with only briefly: parasitology, pathology, prophylaxis. We refer the reader to the specialized books dealing with these topics, and also to the extensive treatises of encyclopedic nature on tropical medicine. We have deemed it best to describe the symptomatology in detail in order to avoid repeating, in the section on diagnosis, many facts which are better classified on a more rational basis than simple experience.

The classification of diseases has been made on a clinical basis. First, the general infections, then the diseases of the various systems: digestive, skin, etc. The helminthiases are studied with the system predominantly involved: e.g., the intestinal parasites, including the schistosomes, with the digestive tract, and the filariae with the skin. Such a basis of classification appeared more practical to us than one of rigid etiology.

We include no bibliography other than the citation of certain authors in the text. A selected bibliography would be too brief and too partial for the expert, and extensive citations are unnecessary for practical purposes. The excellent *Tropical Diseases Bulletin,* which has been edited for several decades by the London Bureau of Hygiene and Tropical Diseases, will provide those readers interested in consulting the sources with a rapid and relatively certain method of finding the best world-wide literature on the subject.

No author of such a text can claim to be exempt from errors of omission. The wide scope of the subject and the necessity of remaining within reasonable limits explain certain gaps. We believe, moreover, that amid the constant evolution of science a work of this sort must remain somewhat conservative. A fact or a theory is not deemed worthy of inclusion unless, as a result of universal confirmation, it has ceased to be the property of any one man or school and has attained classic value. We have, however, mentioned points of view, as yet hypothetic, which may help toward a more complete understanding.

In limiting this volume to the medical practice, we have illustrated it especially with clinical photographs, including, moreover, pictures of the principal parasitic agents, the identification of which permits a positive diagnosis of the disease. We have made a point of using previously unpublished photographs, taken from our private collection, from that of the Antwerp Institute of Tropical Medicine, or kindly lent by Belgian and foreign colleagues.

Since both of us are professors in the Belgian Institute of Tropical Medicine, it is naturally of Africa that we have the widest and most personal knowledge. Nevertheless, we have paid a number of visits to America and Asia so that our interest is not exclusively African. No human science, and least among them, medicine, can limit its interest to any one continent or country. World War II made it strikingly evident that no ocean is wide and that there are no lost islands in the Pacific. The tropics are not more than a few hours by air, no matter from where we start. If a "united world" seems to be a utopian dream to some, a "united medicine" is a present reality of which men of every race and latitude ought to be aware.

It is for this reason that our book is neither the expression of the Belgian school of thought nor a guide solely for Central Africa. It is addressed to physicians and hygienists of all countries who, under the banner of universal medicine, and in every climate, will help build the highways to a healthy and prosperous international community. It is in this spirit that two editions of the same book, one in French, the other in English, will be published at approximately the same time in Belgium and in the United States of America.

A. D. and L. v. D. B.
Antwerp, January 1947

Chapter I

GEOGRAPHIC DISTRIBUTION OF THE SO-CALLED TROPICAL DISEASES

It has been pointed out that there are actually very few diseases which are exclusively tropical. African trypanosomiasis is one such, due to the existence of a vector, the tsetse fly, whose distribution is distinctly limited. Nevertheless, a goodly number of diseases are infinitely more important in the hot than in the temperate climates. In these cases, a vector is often a causal factor (e.g., the mosquito for malaria). In other instances the backward state of public or private hygiene must be held responsible (leprosy, bacillary dysentery). In some cases the greater incidence in the tropics is obscure (e.g., amebic dysentery).

The rise and, at times, the disappearance of diseases, the variations of their distribution, is a historical phenomenon about which we know but little. Whatever the origin of the human race, it is certain that our remote ancestors did not, in the earliest days, show all the diseases of today. These have developed through the ages by the adaptation of parasites and the reactions of the host.

Nicolle has pictured dazzling phylogenic tableaus in which is seen first the transmission of the germ from one animal to another animal or even to man by arthropodes (spirochetes of relapsing fever by ticks, rickettsias of endemic typhus by fleas). Then the spreading is ensured by a vector more closely allied to man (spirochetes of relapsing fever by lice, rickettsias of epidemic typhus by lice). Finally, direct contact may serve to ensure the preservation of parasitic species (spirochetes of syphilis or of yaws, ricketsias of "Q" fever).

These are fascinating syntheses, shaded, nevertheless, by the mystery of the origin and destiny of creatures. In some cases the animal reservoir of virus presents only inconspicuous infections, or as Nicolle expresses it, "unapparent diseases" (yellow fever, tick relapsing fever, fluvial typhus). Sometimes animal infection is more or less evident (plague). In rare instances man is symptomless and the disease appears only in animals (dog's distemper was the first human "unapparent disease" described by Nicolle).

On the other hand, certain cosmopolitan diseases of one or two centuries ago (such as cholera and plague) are limited in these days to the overpopulated regions of the tropics because such regions alone offer a suitable environment for their development. The modern hygienist has reason to fear that, contrariwise, diseases now confined to tropical regions may spread, thanks to air or sea transport, to other warm or temperate regions: an eventual introduction into Polynesia of Anopheles and malaria; a possible spread of yellow fever from Africa to Asia by infected mosquitoes or people transported by air; the possible appearance of schistosomiasis in the United States where receptive molluscs already exist. Contemporary history records the example of the spread to South America of African schistosomiasis introduced by slaves, and the Bancroft filariasis to the southern United States, where the suppression of the slave trade appears to have brought about the disappearance of the parasite. The example of Brazil shows us that modern hygiene is not powerless. It is already known that the recent introduction of Anopheles gambiae in certain Brazilian states has been sufficient to bring about a serious malaria epidemic, but that the hygiene services have succeeded in eradicating the African species introduced.

It therefore becomes very difficult to determine the geographic limits of diseases. Nevertheless, many modern treatises publish maps showing the geographic distribution of so-called tropical diseases. But their exactness is more apparent than real. These maps are too often based on bibliographic information which does not give full guarantee of the accuracy of diagnosis. It was only in 1946, for example, that we learned as a certainty of the existence of Filaria bancrofti in the Congo. Many areas of the globe are still, medically speaking, unexplored, and should bear the legend of our ancient atlases—"terra incognita." Instead, therefore, of making use here of geographic charts (useful, but only approximate) of the spread of the diseases, we have given, for each continent, a list of so-called tropical diseases, placing in italics those which are peculiar to them. Some continents have had to be subdivided into two zones. In these cases, diseases which are common to both regions indicated, are mentioned on the vertical line separating the two columns.

EUROPE

TEMPERATE EUROPE		MEDITERRANEAN BASIN including the shores of the related continents
	General Infections	
Pl. Vivax, Pl. malariae	Malaria	The 3 forms: Blackwater fever, Boutonneuse and Q fevers, Relapsing fever (ticks)
	Epidemic and endemic typhus	
	Relapsing fever (lice)	
Trench fever		
Disappeared actually	Plague	
Tularemia		
	Brucellosis	
		Dengue and Papatacci fevers
		Visceral Leishmaniasis
	Intestinal Diseases and Enterohepatic Helminthiases	
	Bacillary Dysentery	
rare clinically	Amebiasis	
	Cholera (rare since 50 years)	
in the mines	Ankylostomiasis	
Opistorchiasis		Schistosoma haematobium and mansoni
	Skin Diseases and Filariasis	
	Leprosy	
		Cutaneous Leishmaniasis
		Wuchereria bancrofti
		Ulcus tropicum, Desert sore
	Deficiency Diseases	
sporadic cases	Pellagra	
	Scurvy	
	Xerophthalmia	
	Hunger Edema	
	Sprue nostras	
	Venomous Animals	
	Viperidae	Colubridae (Proteroglyphic)

ASIA

WEST ASIA (from the sea to the Indus)		EAST ASIA AND INDONESIA
	General Infections	
	Malaria and Blackwater fever	
	Epidemic and endemic typhus	Tsutsugamushi and other Ricketsial diseases
Relapsing fever (ticks)	Relapsing fever (lice)	
	Plague	
	Tularemia	
	Visceral Leishmaniasis	
	Dengue and Papataci fevers	
	(no yellow fever)	
	Intestinal Diseases and Enterohepatic Helminthiases	
	Bacillary Dysentery	
	Cholera	
	Amebiasis	
	Ankylostomiasis	
Schistosoma haematobium		*Schistosoma japonicum*
		Paragonimiasis
		Clonorchiasis
		Fascioliasis
	Skin Diseases and Filariasis	
	Leprosy	
Bejel		Yaws
	Ulcus tropicum	
		Mycetoma
		Granuloma venereum
	Wuchereria bancrofti	*W. malayi*
	Filaria medinensis	
Cutaneous Leishmaniasis		also in dry parts of India
		Tinea imbricata
	Deficiency Diseases	
	Beriberi	
	Pellagra	
	Scurvy	
		Epidemic dropsy
		Sprue
	Venomous Animals	
	Viperidae	
	Colubridae (Proteroglyphic)	

TROPICAL AFRICA

General Infections

Malaria and Blackwater fever
Typhus epidemic and endemic and other unclassified Ricketsial diseases
African Trypanosomiasis
Relapsing fever (lice and ticks)
Plague, epidemic and sylvatic
Yellow fever epidemic and endemic, also forest form ("jungle")
Dengue
Visceral Leishmaniasis

Intestinal Diseases and Enterohepatic Helminthiases

Bacillary Dysentery
Amebiasis
Ankylostomiasis
Schistosomiasis (Sch. haematobium, *Sch. h. var. intercalatum,* Sch. mansoni)

Skin Diseases and Filariasis

Leprosy
Yaws
Granuloma venereum
Ulcus tropicum
Mycetoma
Filariasis bancrofti
    loa
    volvulus
    medinensis
    streptocerca

Deficiency Diseases

Beriberi
Scurvy
Xerophthalmia
Pellagra
Depigmentation-Edema Syndrome
Sprue is rare

Venomous Animals

Viperidae
Colubridae (proteroglyphic)

AMERICA

<table>
<tr><th>NORTH (Mexico not included)</th><th>CENTRAL (with Mexico) AND SOUTH</th></tr>
<tr><td colspan="2">GENERAL INFECTIONS</td></tr>
<tr><td colspan="2">Malaria and Blackwater fever</td></tr>
<tr><td>Q fever, Endemic Typhus, Brill's disease</td><td>Epidemic and endemic disease</td></tr>
<tr><td>*Rickettsialpox*</td><td></td></tr>
<tr><td>*Rocky Mountain spotted fever*</td><td>*Sao Paulo typhus*</td></tr>
<tr><td>*Bullis fever*</td><td></td></tr>
<tr><td>Relapsing fever (ticks)</td><td>Relapsing fever (lice and ticks)</td></tr>
<tr><td></td><td>*American trypanosomiasis*</td></tr>
<tr><td></td><td>Visceral Leishmaniasis</td></tr>
<tr><td>Sylvatic plague (California)</td><td>Plague</td></tr>
<tr><td>Tularemia</td><td></td></tr>
<tr><td colspan="2">Brucellosis</td></tr>
<tr><td colspan="2">Dengue and Papataci fevers</td></tr>
<tr><td>*Colorado tick fever*</td><td></td></tr>
<tr><td>Epidemic yellow fever (disappeared since 1905)</td><td>Yellow fever, epidemic, endemic, "jungle"</td></tr>
<tr><td></td><td>*Bartonellosis*</td></tr>
<tr><td colspan="2">INTESTINAL DISEASES AND ENTEROHEPATIC HELMINTHIASES</td></tr>
<tr><td colspan="2">Bacillary dysentery</td></tr>
<tr><td colspan="2">Amebiasis</td></tr>
<tr><td colspan="2">Ankylostomiasis</td></tr>
<tr><td>Clonorchiasis</td><td></td></tr>
<tr><td>Paragonimiasis</td><td></td></tr>
<tr><td></td><td>Schistosoma mansoni</td></tr>
<tr><td colspan="2">SKIN DISEASES AND FILARIASIS</td></tr>
<tr><td colspan="2">Leprosy</td></tr>
<tr><td></td><td>Yaws</td></tr>
<tr><td></td><td>*Pinta*</td></tr>
<tr><td colspan="2">Granuloma venereum</td></tr>
<tr><td></td><td>Ulcus tropicum</td></tr>
<tr><td></td><td>Muco cutaneous Leishmaniasis</td></tr>
<tr><td></td><td>Mycetoma</td></tr>
<tr><td></td><td>*Mansonella ozzardi*</td></tr>
<tr><td>W. bancrofti (recently disappeared)</td><td>W. bancroft, Elephantiasis</td></tr>
<tr><td></td><td>Onchocerca volvulus (caecutiens)</td></tr>
</table>

AMERICA (Continued)

NORTH (Mexico not included)		CENTRAL (with Mexico) AND SOUTH
	DEFICIENCY DISEASES	
	Scurvy Pellagra Beriberi	
Sprue nostras		Sprue
	VENOMOUS ANIMALS	
	Arachnidae Viperidae (Crotalinae) Colubridae (Elaps)	

OCEANEA

MELANESIA—NORTH AUSTRALIA		POLYNESIA—MICRONESIA
	GENERAL INFECTIONS	
Malaria and Blackwater fever Endemic typhus, Tsutsugamushi and Q fevers		
	Dengue	
	INTESTINAL DISEASES AND ENTEROHEPATIC HELMINTHIASES	
	Bacillary Dysentery Amebiasis Ankylostomiasis	
	SKIN DISEASES AND FILARIASIS	
	Leprosy Yaws	
Granuloma venereum		
	Ulcus tropicum Tinea imbricata W. bancrofti	
	DEFICIENCY DISEASES	
Beriberi		
	VENOMOUS ANIMALS	
Colubridae		

Chapter II

THE WARM CLIMATES. THEIR PHYSIOLOGIC AND PATHOLOGIC INFLUENCE

1. The Warm Climates

Everyone knows what is meant by warm climates. They are not necessarily tropical in location. Several types exist, varying according to the local conditions. Three principal varieties may be distinguished.

(a) The hot, dry climate of desert and sub-desert regions which are for the most part situated outside of the tropical zone. In view of this geographic situation, the seasons are well defined. In summer the days are very hot, but the nights are relatively cool because of the intense radiation. It is in these regions that the highest maximum temperatures are recorded (45–50 C.). The winter may be very cold (type Iraq and Iran).

(b) Climate with alternating wet and dry seasons. These are the true tropical climates where the different seasons are more accurately determined by the rain-gage than by the thermometer. The monsoon regions also show this difference between seasons, the maximum temperatures being recorded shortly before the rainy season.

In the tropics the dry season corresponds to the winter, that is to say, the time when the sun is lowest in the sky. The "cloud ring," which is the generator of the rains, follows the sun. As a result, minimum temperatures are recorded, at least at night. During the day, as a result of the absence of rain and clouds, the maximum temperature may be high In Lower Congo (4–5° latitude south, the dry season is from June to September), the presence of the cool sea current from Benguela gives rise to morning mists and to a fine haze which considerably lowers the diurnal temperature, especially until noon.

The rainy season corresponds to the time when the sun is at the zenith and when the area is therefore visited by the "cloud ring" or "pot au noir." Here solar radiation is maximal, but the thick haze and the frequent rains often lower the temperature. It is easy to see that, in the course of the tropical year, the sun is at the zenith only once at a point about 20° north or south of the Equator, but twice at a point situated 5–6° north or south of the Equator. From this there result climates with either one or two dry seasons, but the short dry season is of slight practical importance. In this type of climate the seasonal and daily variations of temperature are moderate, and the humidity is usually high even in the dry season (type Leopoldville and Lagos).

(c) Climate with an insignificant dry season continually hot and damp. Here the seasonal and daily variations are minimal. Frequent rains and thick clouds tend to limit the maxima (Equatorial type).

Influence of Altitude. This is very marked, there being roughly a fall of 1 C. in temperature for each 180 meters rise in altitude. High altitude resorts are numerous in various tropical countries. Coquilhatville in the central Congo basin (0.3° N., altitude 320 meters) has a temperature varying between 17 and 35.6 C., while Butembo (latitude much the same as the former, but altitude 1800 M.) has a temperature varying between 6 and 27 C.

Influence of Climate. The most important factor is heat, but it is necessary to take into account as well the humidity and the air currents. It is known that the more damp and motionless the air, the more difficult is heat regulation. Damp heat predisposes to heat stroke (due to a failure of heat loss) or to heat exhaustion. Dry heat predisposes to dehydration and to cramps due to an upset in ionic balance.

The atmospheric pressure plays a less well defined role. Variations in this factor (mountains, aviation, etc.) considerably limit the activity and habitat of man. Man rarely lives above 2,000 meters. The extreme limit, however, of human settlement is between 4,000 and 5,000 meters (Tibet and the Andes), and there are towns above 3,000 meters.

Little is known about the influence of electrical phenomena.

Wind plays an important part in moderating the action of heat (trade winds and land and sea breezes), sometimes exaggerating it (sirocco), causing excessive desiccation and dust formation (harmattan, khamsin), or bringing rains (monsoons).

Rain is an important factor in climatology. In tropical regions it is a common cause of a fall in temperature. In certain regions whole days may be fairly cold by reason of fine continuous rain, quite different from the classic tropical downpours. The clouds which accompany the rain are an effective screen against solar radiation.

Light, by special virtue of its radiations of long wave lengths, is the generator of heat, and thus the sun may cause heat stroke. By its short radiations, light may produce in fair skins an erythema, sometimes vesicular. Later on, a protective pigmentation may develop, which, however, is more marked in dark complexions. The erythema may be accompanied by general symptoms. Intensive reverberation (snow, sand, water) may cause amaurosis. Fair skin usually supports radiation badly. A chronic alteration may even produce epithelioma. Negro albinos are most sensitive. Solar dermitis is not peculiar to the tropics.

2. Physiologic Adaptation

It is difficult to find in the European* any great physiologic variations after he has lived for some time in the tropics. They rather occur at the beginning of his stay.

Variations of basal metabolism (decreased by 5 to 10 per cent) and of body temperature (on the increase) are slight and, moreover, not constant. As regards the circulation, there is a certain lowering of blood pressure, the mechanism of which is uncertain. The blood volume may, however, be slightly increased by dilution in response to the needs of the skin (congestion and perspiration). The pulse is somewhat accelerated.

There is little to note concerning the digestive system except for a slight diminution of the appetite, especially for foods of high caloric value.

Thirst varies according to muscular activity and whether the climate is dry or damp. In the former case the daily water requirements may rise to four to eight liters or more (salt in proportion).

Experiments made on healthy subjects in the heat chamber show that there is a fairly rapid adaptation to physical work. Starting the second day, it is complete by the seventh or eighth. The tachycardia, the elevation in body temperature, and the malaises all decrease. Perspiration increases but the chloride concentration varies greatly from person to person and even in the same individual. Perspiration commences more readily with a slight rise in rectal temperature. An increase in skin temperature also takes part in the perspiration mechanism. When it reaches 34.4 C. sweating starts.

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* By "Europeans" we mean individuals of European origin, direct or indirect, who for centuries have been adapted to temperate climates. This definition, therefore, includes North Americans, New Zealanders, South Australians, etc. "The white races" is a definition less restrictive as it includes certain natives of warm regions: Ibero-Americans, Iranians, Indoaryans, etc.

Excretion shows no particular departures from the norm except for a considerable concentration of urine, responsible for cristalluria and calculosis, and requiring special attention in giving sulfonamides.

Information concerning the endocrine glands is still indefinite. It has been observed that sufferers from hyperthyroidism support hot climates badly. The role of the suprarenal cortical hormone is insufficiently established. It has been said without proof that the reproductive functions may be established earlier in European women living in the tropics. The physical type tends to be slender among children brought up in the tropics, but the same increase in size occurs elsewhere, including temperate regions.

According to Mills, on the contrary, the stature of European children would decrease in the tropics, menstruation would be delayed and fertility diminished. The precocity of menstruation among African native women has been exaggerated.

The skin plays an essential role in heat regulation. Icthyosics and people suffering from agenesis of the sweat glands are not fit subjects to live in hot climates. The dark skins of various races absorb more heat, but in these cases perspiration is more active and more efficient. The Negro has more sweat glands per unit of body surface than the white man.

It is in the realm of the psycho-nervous system that the most frequent difficulties of adaptation arise. In addition to the climate, social, intellectual, and moral conditions are responsible. It is especially the monotonous climates without appreciable variations either from day to day or season to season which are harmful, in particular causing insomnia. Here civilization can play a great part by providing entertainment, sports and, to speak of another and important factor, air-conditioning. Holidays in the mountains or, better still, in one's homeland are necessary from this point of view.

The people best adapted to tropical life are young adults (25–40 years), of sound constitution, presenting no organic or functional abnormality. Considerable attention should be paid to mental balance. From this point of view, a certain sublimation of interests such as philanthropy, religion, science, patriotism makes a successful adaptation more sure. Success, however, finally depends on the ability to avoid tropical diseases by sound prophylaxis and efficacious therapy (development of the medical service).

Racial acclimatization does not appear to be impossible. The examples of Espirito Santo (German colony in Brazil), Queensland, and also Dutch Guiana are, on the whole, encouraging.

Manual work and competition appear to play a role of prime importance in maintaining the vitality of the race. It is, however, wise not to attempt this acclimatization except in well chosen regions where the climate is tempered somewhat by altitude, etc.

The absence of native population, a great rarity, would be a favorable circumstance, as the immigrants would then have to do all the work and the chances of infection would be considerably reduced (malaria, for example).

3. The Hygiene of the European in the Tropics

A careful medical examination is essential before departure and, moreover, is insisted upon by most employers. It enables one to exclude any serious affections and any visceral or functional anomalies. One should not neglect to put the teeth in good order, to test the visual acuity, and to prescribe the appropriate glasses (two pairs). Various vaccinations are either compulsory (smallpox and yellow fever) or advisable (typhoid, etc.).

Clothing. The naturalist, the hunter, etc., who intends to wander far from the beaten track should make a point of going over his equipment with a man who knows the proposed region. The following remarks are of value for the more usual class of individual who lives a rather sedentary life which differs from that in temperate countries only by reason of the climate.

It is advisable to use light material which does not interfere with heat loss. White or tinted (khaki) cotton drill has the advantage of lightness and ease of washing. "Palm-beach" suits are also comfortable. Women have at their disposal all the range of summer materials. When traveling they often find shorts or slacks more practical than skirts.

The style of clothing does not matter much, the short sleeved jacket, often called "Safari"* or "Sahara," being a practical garment. A shirt with attached collar, often with short sleeves, does not have the same pockets which are so useful to the traveler. The "Safari" is convenient chiefly when traveling and the ordinary shirt when on a station. Shorts are usually preferred to long trousers. They are cooler but afford little protection against insects. A finely woven undershirt is helpful to those who perspire freely. Socks or short stockings as well as shoes are generally the same as those used elsewhere. Sandals with leather thongs are obviously very cool, but they expose the wearer to chiggers. Light leather boots, the so-called "Madeira boots," afford useful protection against mosquitoes and flies. Flannel waist bands should be reserved for soldiers, etc., who have to sleep in bivouac. The ordinary traveler nearly always sleeps on an ordinary camp bed with bed clothes. A raincoat is often useful: rubber, however, is normally too warm, and water-proof cloth is rarely effective. The new plastic materials are at the same time light and water-proof.

It must never be forgotten that it sometimes becomes very cold in the tropics, usually during rainy weather and at night or at high altitudes. It is therefore necessary to provide oneself with overcoats and blankets. At high altitudes clothing is essentially the same as in temperate or even cold climates.

A good mosquito net (7 holes per cm. length) is an essential part of all tropical equipment (see *Prophylaxis* of Malaria, Chap. IV).

As for headwear, fashions are rapidly changing in the majority of tropical countries. If one reads the literature of twenty to thirty years ago, be it fiction or medical (chiefly French), one gathers that the very act of exposing the bare head even for a few moments to the tropical sun involves mortal danger. However, there were, even then, a few heretics. This heresy of yore appears little by little to be conquering the tropical world of which, let it be said, certain parts (South America) had never adopted the sun helmet. Actually it is quite common to see on the Equator at low altitude, for example at Stanleyville and Leopoldville on the Congo, racially pure Europeans walking about bareheaded. It does not appear to produce any definite trouble, in particular no greater incidence of heat stroke. It seems to us, however, that it is better to be prudent. It is obvious that for short distances the danger is negligible. It is necessary in the case of long treks to take account of individual differences, and we still advise a good sun hat of which the pith helmet remains the most effective. In certain countries (Iraq, Iran) the helmet is compulsory. The panama hat can also be recommended. When the surroundings are cool (mountains, seaside, coastal regions), it seems that direct exposure of the head to the sun does not carry any danger. It is the same in the case of swimmers. On the other hand, in very hot countries exposure of the head to the sun can bring about a rise of body temperature. Experiments on animals exposed to the sun, with or without artificial cooling of the body, confirm this view.

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* A Swahili word meaning "expeditionary travel."

Eyes. The wearing of smoked glasses is almost the rule and is recommended chiefly for dry, very bright districts.

Food. There is nothing exceptional to note about the nature of the food for the European in the tropics. It must be varied, adequate in quantity, rich in vitamins, and contain enough residue and water (fruit and vegetables) to combat insidious constipation due in part to dehydration. It is necessary, above all, to see that the food is properly prepared and that the servants are not germ carriers. One tries to prevent, by all means available, the access of flies to the food. The general use of refrigerators represents a considerable forward hygienic step. Many residents in the tropics wash salads, etc., with chlorinated water or permanganate solution. This measure is effective against bacteria, but it is not always effective against amebic cysts. In the case of an intestinal epidemic it is better to abstain from fruit and raw vegetables excepting those which can be peeled or disinfected effectively. Wines, beer, and spirits (straight or diluted) should be consumed only in very moderate amounts and not during the hot part of the day. In spite of considerable progress in this matter too many alcoholic drinks are still consumed in warm countries. Water should be boiled, then aerated and filtered.

Most Europeans keep to their usual customs concerning meals: breakfast about 8 A.M., lunch about 12 noon–1 P.M., dinner about 7–8 P.M. Certain people prefer to substitute some fruit for lunch, with tea and biscuits at 5 P.M. if desired. This is a practice to be recommended when one works between noon and 2 P.M.

Cleanliness. This is particularly important. It concerns the underclothes, to be changed every day (sometimes more frequently), the body (bath or shower daily), the house and garden. As for baths, it is difficult to decide between the advantages of the warm as compared to the cold. The tepid bath is more restful and more cleansing. The cold sponge in the morning is as useful in warm climates as it is in temperate climates. According to our experience, those who are convalescing from malaria, etc., should abstain from cold baths or showers.

Exercise. This is necessary in the tropics, as elsewhere, for sedentary people. It must be taken at a suitable hour in the morning (which is rarely possible due to the necessity of utilizing these hours for work) or in the afternoon. The tepid bath should follow this exercise.

Siesta. A midday nap seems useful for certain people but must not be too prolonged.

Organization of the Day. The day's work should begin early for full utilization of the cooler hours.

In Congo, just as in many countries, one finds different methods of dividing the working hours,

(1)	6–8 A.M.	Work
	8–8.30 A.M.	Breakfast
	8.30–12 noon	Work
	12 noon–2 P.M.	Lunch and siesta
	2 P.M.–4.30 P.M.	Work

This system is practiced but little in big towns. One of the following is then more definitely indicated.

(2)	7.30 A.M.–12 noon	Work
	2 P.M.–4.30 P.M.	Work
(3)	8 A.M.–2 P.M.	Work

This last system is convenient in very hot countries. It makes certain of an excellent siesta during the most trying hours and enables one to play games or take part in other necessary recreation after 4.30 P.M.

The house plays a role of first importance in the individual's adaptation to the climate. It must, both by its design and by the thickness of its materials, be as poor a conductor of heat as possible. In the absence of heat-resisting walls of the hollow type, bricks in a thick bed of mortar are probably the simplest and best. Beaten earth is very cool but not very durable. Concrete has the advantage of keeping away termites. If bricks are used it is necessary in every case to make a large cement foundation to avoid termites which are so destructive to buildings. The best roofs are made of tiles, fibro-cement, or other materials which are poor heat conductors. Ventilating spaces are interposed between the roof and the rooms.

There is a marked tendency to abandon the verandah for economic or esthetic reasons. Although it shades the rooms too much, it does provide an efficient protection against the heating of the walls especially on the west side of the house. In certain countries the protection of the verandah against heat is made even more effective by the use of straw or linen window blinds, provided with sheets of highly reflecting metal. In Congo the latter precaution appears to be scarcely necessary except on the west side. If one sacrifices the verandah, one must replace it by overhanging roofs or with awnings above the windows. At any rate, contrary to the general belief of colonials, the verandah is never the ideal spot in which to stay in warm countries. During the day it is hotter than the inside rooms, and in the evening it is less cool than an unscreened terrace. The latter, however, has the disadvantage of not being mosquito-proof.

The inside rooms should be large and high with closable ventilators (also mosquito-proof). Large cubic volume enables one to conserve the cool night air during the day. From 1 to 4 hours after sunrise, doors, windows, and ventilators must be closed in order to maintain this coolness. During the night, on the contrary, they are opened as wide as possible in order to cool the air and the walls. This excellent but little used system is employed only in districts with relatively cool nights. If the nights are nearly as warm as the days, only "air-conditioning" can solve the problem. This method cannot be insisted upon because it requires special technical equipment and, in many cases, depending upon the system best adapted to local conditions of humidity, etc., an economical supply of electricity. The cooling and drying of the air must be studied separately in each case.

Tents. A tent, very hot during the day and very cold at night, is obviously to be used as little as possible for human habitation. However, if the tent is to remain in situ for a certain time, its comfort can be considerably improved by building over it a light roof of straw or palm fronds.

4. Pathologic Conditions Caused by Heat

When man is exposed to high temperatures there is a decrease in his ability to lower his metabolic rate and thereby to diminish his heat production. Instead, he increases his heat loss as much as possible by congestion of the skin, bringing about increased radiation and conduction (if the external temperature permits this), and most importantly by an increase in evaporation from the skin and to a lesser degree from the lungs. This evaporation from the skin necessitates, of course, ample quantities of water and salts. Any condition which depresses evaporation, such as high humidity of the atmosphere, absence of movement of the air, and thick clothes, makes heat regulation difficult.

Geographic Distribution. Microclimates (industrial vapors, human respiration, forests, etc.), above all those found in industry in every country, upset heat regulation. Moreover, accidents (see page 16) are met with occasionally in temperate countries which have a very hot summer, particularly in cities (Eastern United States). Certain hot countries are especially notorious: Iraq, Iran, North and Central India, the Red Sea area. With the exception of the latter, these are, generally speaking, countries with very hot but not very humid climates. Thus in Iraq the maximum temperatures encountered are 51.6 C. and in tents 60 C., with nights a little better (31 C. and 42 per cent humidity). If such conditions persist for several consecutive days, the danger is great.

In lower Central Africa the temperature is rarely very high (35–37 C.), but the humidity is exceedingly great (more than 90 per cent). Heat stroke, however, is manifestly rare there. This would seem to indicate the predominant role played by upset of water and ionic balance in the pathogenesis of various conditions.

Etiology. The sun is the sole external source of terrestrial heat. Its rays are distributed by radiations of very short wave length (invisible, ultraviolet, between 1,000 and 4,000 Å), by average radiations of the Newtonian spectrum (from 4,000 to 8,000 Å) and by radiations of long wave length (infra-red, from 8,000 to 30,000 Å).

The fate of these radiations in the atmosphere is very different. The ultraviolet, and especially the abiotic among them, are absorbed by the ozone which is particularly abundant in the upper atmosphere. This substance is supposed to be in a quantity of less importance in the tropics. In contrast to this, the factor of opacity (dust particles) is often greater there in the lower atmosphere. These two factors counterbalance each other in a variable but not very precise way. The diffusion of short wave length components (blue) of visible radiation is greatest in the upper atmosphere which owes its particular color to this phenomenon. The infrared rays are greatly absorbed by water vapor (dry air is, on the contrary, diathermane). The absorbed rays warm the atmosphere (transformation of radiant energy into kinetic molecular energy).

General nebulosity must also be taken into account, for it greatly lowers the temperature. The "global" radiation is measured by the energy brought to the horizontal unity of surface by direct solar radiation and by radiation from the sky.

In central Congo the energy collected per tranquil day attains 545 Gm. cal. per square cm., but remains on an average at 300, a number scarcely surpassing the September average in Paris. The annual insolation in the central forest basin of Congo is 1861 hours at Yangambi (i.e., 42 per cent of the total astronomical possibility), it mounts to 2,678 hours (i.e., 61 per cent) in the savannah of the Katanga, to 3,670–3,900 hours (84–89 per cent) in desert climate (Helouan in Egypt and Yuma in Arizona). By way of comparison, Brussels has 1,614 hours (37 per cent), and Buea in the Cameroun, in a very rainy district, has 950 (22 per cent) according to Bernard.

The quality of the soil and the type of vegetation are not without a certain influence. The humidity depends on either the climate or the microclimate. Absolute humidity is the weight of water contained in the unity of volume of the air. The relative humidity is the percentage of this absolute weight to the weight necessary to reach saturation at the temperature under observation.

Movement of air varies according to meteorological or to industrial conditions (ventilators). The relation between temperature, relative humidity, and the movement of air determines the *effective temperature*, i.e., the temperature which acts upon man. Particular attention must be paid to the maximum temperature recorded on the wet-bulb thermometer. (The degree of difference between the readings on the wet and dry bulb thermometers is in inverse proportion to the relative humidity.) A temperature of 31–33 C. recorded on the wet-bulb thermometer should be considered a warning signal.*

A man, motionless and trunk naked, will support a temperature of 31–32 C. on the wet-bulb thermometer in still air. If there is a current of air 3 km. per hour, the limit reaches 33.9 C. In still air a temperature of 37.7 C. is tolerated with 90 per cent humidity, 48.8 C. with 40 per cent, and 60 C. with 15 per cent humidity (readings on the dry-bulb thermometer).

The harmlessness of dry heat must not, however, be exaggerated. At Bagdad, in a dry country, a temperature of 43.3 C. can cause trouble and 48.9 C. is definitely dangerous. It is here that loss of water and salt enters the picture. It has been observed in India that at a temperature of 40 C. and a relative humidity of 47 per cent during a 15 km. march there is a loss of 3 to 4 liters of water and a fall in blood chlorides from 500 to 417 mg. per 100 cc.

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* L. Hill recommends the use of the "Kathathermometer," which measures the loss of heat of a given surface at a temperature of approximately 37 C. It involves an alcohol thermometer of great size which one sets at 100 F. (37.78 C.) and then records the time taken to read 95 F. (35 C.). The time obviously varies inversely to the cooling power of the air. Used dry, the thermometer measures the loss of heat by radiation, conduction, and convection. Used wet, it measures cooling by evaporation.

It is known that in the course of muscular work the greater part of potential energy liberated appears in the form of heat. Thus the influence of profession is evident (soldiers, stokers, etc.).

Clothing which hinders heat loss increases the danger and was evidently the cause of numerous former "epidemics" in India, etc.

Alcohol is an aggravating factor on account of its metabolization, and the diminished resistance of the subject.

Several diseases, in particular those with diarrhea and vomiting, increase the risks of accidents through dehydration.

Men, as a result of their professions, are more exposed than women and infants. and the elderly are more susceptible than adults (insufficiency of thermoregulation or circulation). The reputation of their resistance to heat is one reason for the engagement of members of the colored races as stokers, etc. In fact, however, in the United States, Negroes are often affected.

Pathogenesis. The accidents caused by heat present themselves under three degrees of increasing severity. The second and third syndromes, however, may be interchangeable.

1. *Ordinary syncope:* of sudden onset, etiology not definitely determined, where there is no ionic upset but simply a temporary failure of the vasomotor (type 1) center.

2. *Heat exhaustion:* a condition in which circulatory trouble is due to hydroionic upset (dechloruration and dehydration following excessive sweating). The heat regulating center is not yet knocked out of action, and the temperature remains within limits compatible with life.

It is possible that the condition is in reality more complex and more variable. During these last years, various authors in different continents have described disorders connected with "heat exhaustion" but which differ from the latter by insufficient perspiration (the patients are usually recently cured of prickly heat), by polyuria and a lesser degree of disturbance in the field of dehydration and dechloruration. (Type 2) Instances of polyuria were observed during hyperpyrexia (Ladell, Waterlow, and Hudson, 1944). Shepherd has described in Iraq (1945) a subacute type with moderate but prolonged fever, vomiting, nervous and psychic disorders progressing to a point of maniacal agitation. The mechanism is ill defined.

3. *Heat stroke:* characterized by a considerable failure of heat control. Whether for the reason that evaporation becomes impossible on account of excessive relative humidity or that the mechanism of sweating fails (prodromal anhidrosis is quite often seen), the body temperature rises steadily and progressively and may reach 43 to 45 C. It is possible that such high temperatures produce, as a direct result, alteration of certain proteins, particularly in neurones and diverse parenchymes. Besides this, hydroionic upset may be present: hypochloremia, lowering of alkali re-

serve, excess of blood lactic acid, increased percentage of hemoglobin and red cell count (dehydration). Uremia and hyperglycemia are more rarely encountered. The urine is sometimes poor in chlorides. If one adds 5 drops of nitric acid and 3 drops of a 1 per cent solution of silver nitrate to 5 cc. of normal urine, a dense precipitate is produced. However, in this condition, there is either no precipitate or only a faint cloudiness. The urine occasionally contains a trace of albumin. The cerebrospinal fluid is under pressure but is normal.

Pathology. In heat exhaustion, if fatal, the sole postmortem sign is vascular congestion. In heat stroke there is early but fleeting postmortem rigidity (sometimes this sets in even before death), cyanosis, congestion, ecchymoses or petechial hemorrhages of the viscera, brain, and serous membranes.

The right heart is dilated, the left contracted. Petechial hemorrhages have been noted in the brain, being particularly abundant in the walls of the third and fourth ventricles and hypothalamus.

Microscopically there are areas of degeneration in various organs including the cerebral and cerebellar neurones. These alterations are partially postmortem. There is edema of the lungs and of the brain, the vascular walls being swollen and surrounded with fluid.

Symptoms and Treatment. (1) The mildest form, syncope, needs little exposition. The patient is motionless with a small, weak pulse, shallow respiration, subnormal temperature, and normal urine.

The prognosis is excellent, recovery is rapid with occasionally sticky sweats, and a certain degree of dullness. Treatment is simple: Lay the patient down in some cool and airy place, apply cold wet compresses to the face, provide for inhalation of stimulating vapors (ether, vinegar, smelling salts).

(2) Heat exhaustion (Collapsus thermique) apparently attacks particularly asthenics with low blood pressure. The onset is sudden, or, more rarely, preceded by two to three days of malaise. The patient is in a state of shock, weakness, apathia, low blood pressure; the skin may be dry or drenched with sticky sweat; muscular irritability and cramps (26 per cent), vomiting (70 per cent), and drawn features are noted. There is oliguria and the urine, as well as the blood, has a low chloride content. The blood is concentrated. Temperature is usually normal orally and a little raised rectally. More rarely there is an evident febrile reaction (39 C.). As the patient recovers there is mild fever which persists for from two to three days. Headache is always a prominent symptom and may persist for from eight to ten days. The prognosis in this type of case is usually good.

Treatment. The patient should be kept in a suitable environment at a temperature of 23–24 C. He should be laid flat and the foot of the bed raised if necessary. Infusions of saline and glucose are given intravenously if required, care being taken not to overload the circulation and thus produce pulmonary edema. A balance of intake and output must be observed. Plasma has also been recommended, and cardiac stimulants may be indicated.

(3) *Heat stroke** (Coup de chaleur, Hitzschlag) is, contrary to the other syndromes described, a complete failure of the heat regulating center with, at the same time, an upset of ionic balance. It is to be observed especially in pyknotics, hypertensive subjects and alcoholics. There is always prodromal malaise, fatigue, headache, and excitement. There is oliguria (frequently, but with small quantities), and sometimes a low chloride content.† Anhidrosis is an important early sign, justifying immediate treatment. The patient is usually unconscious, the face congested or cyanotic, the skin dry and burning hot, the pulse bounding and quick. The respiration is stertorous and the temperature very high, reaching 42 to 45 C. Above 42 C. coma is constant, and a temperature at this level for over two hours means a grave prognosis. The pupils are contracted.

Cyanosis, viscous sweat, weakening of the pulse, dilatation of the pupils, increasing respiratory difficulty, absent knee jerk, loss of sphincter tone are all grave signs of approaching death which supervenes in 30 per cent of cases. Delirium and convulsions also carry a serious prognosis.

The aim of treatment in these cases is to reduce the body temperature to within reasonable limits, i.e., 39 C. One should place the patient in a cool, well ventilated or, even better, air-conditioned room. Room temperature, beginning at 15 C., should be raised to 24 C. when recovery sets in. Recourse may be had to physical methods of cooling, such as cold sponging, wet pack, washing the head with cold or iced water. A semi-sitting position is to be preferred. Cardiac stimulants are almost always indicated. Venesection followed by injection of bicarbonate is advised by some authors. Castellani recommends the removal of a large quantity of cerebrospinal fluid. Oxygen may be useful where cyanosis is present. Intravenous injections of saline are rarely necessary, except in severe dehydration and hypochloremia.

(4) *Heat cramps.* Although these are sometimes associated with heat exhaustion they are also found alone, especially in fit subjects doing hard physical work and sweating profusively. An excessive loss in chlorides causes painful muscular cramps with hypochloremia and hypoglycemia. The condition may lead to the previously described forms. Treatment consists in providing saline (0.1 to 0.2 per cent) with glucose. At least 500 cc. of 0.1 per cent saline per hour are required.

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* The term "sun stroke" should be abandoned. It refers either to heat stroke due to solar radiation or to solar dermitis from ultraviolet radiation between 2,800 and 3,100 Å.

† According to Waterlow (1947), hypochloruria would not be part of what is strictly called heat stroke, but would be characteristic of heat exhaustion (hypochloremia, dehydration, anuria, uremia).

Prognosis. We have said that the gravity of the prognosis increases progressively from good in syncope to serious in exhaustion. It is always grave in heat stroke (the morbidity of which is about 30 per cent). It is also following the latter syndrome that pulmonary and psychoneurotic complications are seen—complications which may cause prolonged or definite invalidism. The severity of the prognosis varies directly with the temperature: 8 per cent of deaths with 41.6 C., 29 per cent with 42.7 C., and 69 per cent above that (Rogers).

In 1942, 1,405 cases of heat exhaustion were recorded in India with 27 deaths among English troops and 255 cases with 13 deaths among Indian troops, which means roughly 30 times more cases among the English but a lowered incidence of fatality. One hundred and seventy cases of heat stroke with 34 deaths were also encountered among the English and 129 cases with 62 deaths among the Indian troops (Marriott 1947).

Diagnosis is usually made clear by the etiologic conditions. Apart from this, however, diagnosis from coma with fever is always difficult and, in tropical countries, one must always think of malarial coma (see section on Malaria, Chap. IV).

Consideration of the prodroma is worthy of attention: Malaise, rise of temperature, anhidrosis in particular. Examination of the urine may be useful. The following is a method for measurement of chloride content:

1. Ten drops of urine are placed in a test tube.
2. Add one drop of 20 per cent potassium chromate.
3. Add silver nitrate (2.9 per cent) drop by drop (from the same dropper as used in (1) until the brown tint of silver chromate appears.

The number of drops added equals the number of grams of NaCl per liter. With the help of this method, preventive treatment can be applied in time.

Prophylaxis. The organization of the day's work, artificial ventilation, suitable clothing (trunk bare while working), and air-conditioning are valuable preventives. A sufficient quantity of fluid is given: saline 0.15 to 0.25 per cent up to 4 liters and more daily (workers on the Boulder Dam, U.S.A., drank up to 18 liters per day). The fluid intake needs of patients and operated cases must be met by artifical methods: nasal tube (Ryle's) rectal drop to drop, parenteral injections. Thirst does not provide a reliable indication.

Solar dermitis is hardly peculiar to damp tropical regions. As said before, there is no particular abundance of ultraviolet there. Besides, erythema is produced by radiation inferior to 0.32 micron. These rays absorbed by the cells of the mucous body of Malpighi are the cause of an erythema with swelling, sometimes vesiculation, followed by desquamation. Subsequently a protecting tan and hyperkeratosis set in. The skin of colored races is considerably less sensitive than the white to solar dermitis.

Chapter III

THE COSMOPOLITAN DISEASES IN THE TROPICS

IT IS necessary, for reasons which will be apparent, to consider separately the immigrant population, especially the "Europeans," and the native population, mostly colored.

The former was, until recently, composed principally of selected male adults and it is understandable that cosmopolitan diseases were rare among them. Venereal diseases, consequences of alcoholism and psychoneurotic disturbances due to unfavorable living conditions were common. Actually, with the increase of the immigrant population in women, children and older people, the pathology of these Europeans now comes closer to that of their birthplaces (with tropical diseases in addition). Most of the diseases have invaded the entire surface of the world. Nevertheless, a high standard of living, vaccination and efficient medical care, limit in this population various parasitic diseases present among natives, e.g., typhoid fever, epidemic typhus, bacillary dysentery, plague, cholera, and intestinal helminths. Tuberculosis, a cause for nonemployment or repatriation, is relatively rare.

A warm climate, outdoor life and larger house space make respiratory infection, to a certain extent, less frequent. Circulatory pathology presents no special deviations. Rheumatic fever is rarer in warm than in cold countries.

In connection with the digestive system, one notices the frequency of constipation (dehydration, diet poor in residue, lack of exercise), of dyspepsia (abuse of spices and alcohol, nervousness), of hepatic congestion (alcohol), hemorrhoids, etc. Renal concretions are supposed to be more frequent than in the temperate zone (dehydration). Pregnancies are more exhausting. Quinine sometimes causes excessive menstrual fluid.

Dutch writers point out the frequency of light glycosuria among the residents of Indonesia. The psychonervous equilibrium remains rather unstable and often results in a number of repatriations and career interruptions.

The macerated skin is easily infected: papulous miliaria (lichen tropicus, prickly heat) is a tropical disease. Pyodermatitis extending to an ecthyma and mycoses are frequent. On the other hand, an infection as common among natives as yaws is completely absent among European immigrants. Leprosy is seen occasionally.

In short, tropical pathology in the immigrant is definitely on the downtrend before the progress of medicine. Military expeditions offer greater risks and an impeccable organization alone can limit infection and disease. A constant decrease in mortality is noticeable. The example of the Congo, opened up late to civilization, is typical.

Mortality per thousand Europeans:

1885–1890	91.0
1900–1908	51.5
1909–1920	28.17
1921–1930	13.29
1931–1935	9.00

It is understood that, with economic expansion, the population includes more and more children and aged people. Similar or more favorable statistics are to be found in most warm countries among European immigrants.

The study of the native population of primitive culture (Negroes, Melanesians, certain Asiatics, Amerindians, etc.) is most informative. The life of many primitive peoples presents common characteristics: agricultural occupations, very slight physical and even less mental strain and incentive, vegetarian alimentation, scarcely any animal proteins except where game or fish abound, open air life. Personal hygiene and, more especially, cleanliness in the house are generally insufficient. Crowded conditions due to restricted living quarters are omnipresent. Alcoholic excesses are rather occasional. Tobacco is widely used and so are sometimes substances which exert an influence on the psychism (hemp, coca, etc).

Exaggerated unconcern often leads to famine or semistarvation. Animist belief or fetishism results sometimes in irrational fear or wrong ideas on the origin of diseases.

As a result of lack of hygiene, perhaps also because of constitutional factors or dietary deficiencies, the primitive man is generally exceedingly susceptible to various infections. The result is a high mortality rate (influenced by a high infantile mortality rate due to ignorance, etc.) and a low average longevity.

Noninfectious diseases, so important in civilized areas, are rare among primitive peoples. Allowances must here be made for the composition of the population which includes fewer aged people.

The pathology of the more or less Europeanized natives, laborers, clerks, administrative agents, etc., is slightly different. Experience proves that the native stands his sudden introduction to industrial labor rather badly and much illness lies in wait for him. On the other hand, however, he often enjoys the benefits of a good medical organization. Here interest is a much more certain incentive than philanthropy. Mortality is finally reduced to a reasonable level, which in any case is lower than that of natives at large. To quote the statistics of the Union Minière du Haut-Katanga (copper mines and refineries in South East Congo):

Mortality per 1000 (Black laborers and their families):

1925–1929	45.9	1935–1939	15.0
1930–1931	25.5	1940–1944	12.3

Finally there are whites, settled for generations in warm countries, who may in fact be considered as true natives. Their pathology varies greatly according to their location and standard of life. Among these are to be found the "poor whites," for whom a vicious pathologic and economic circle results in a low state of health. The pathology of this class is comparable to that of the colored native.

The cosmopolitan pathology of the tropics is rapidly covered by emphasizing the situation existing among the natives. It must be confessed that this pathology is still only imperfectly known, due to a relative shortage of doctors, scarcity of necropsies and surgical intervention, tendency of natives to consult only in cases which attract great attention as well as the specialization of doctors in diseases of high social importance (endemo-epidemics).

1. GENERAL VIRUS INFECTIONS

(A) SMALLPOX (VARIOLA, POCKEN)

This disease was once very widespread, but has declined since the introduction of vaccination. Nevertheless, serious epidemics of "Variola major" are still to be observed in certain countries (East Asia). Elsewhere, as for example in Congo, "Variola minor" and Alastrim (milk pox), which does not seem to be justifiably distinguishable from the former, are more often encountered. Smallpox is not peculiar to the tropics. Alastrim is a benign form of smallpox with a mortality of about 1 per cent or less with very little suppuration of the eruptive elements which are sometimes rather small.

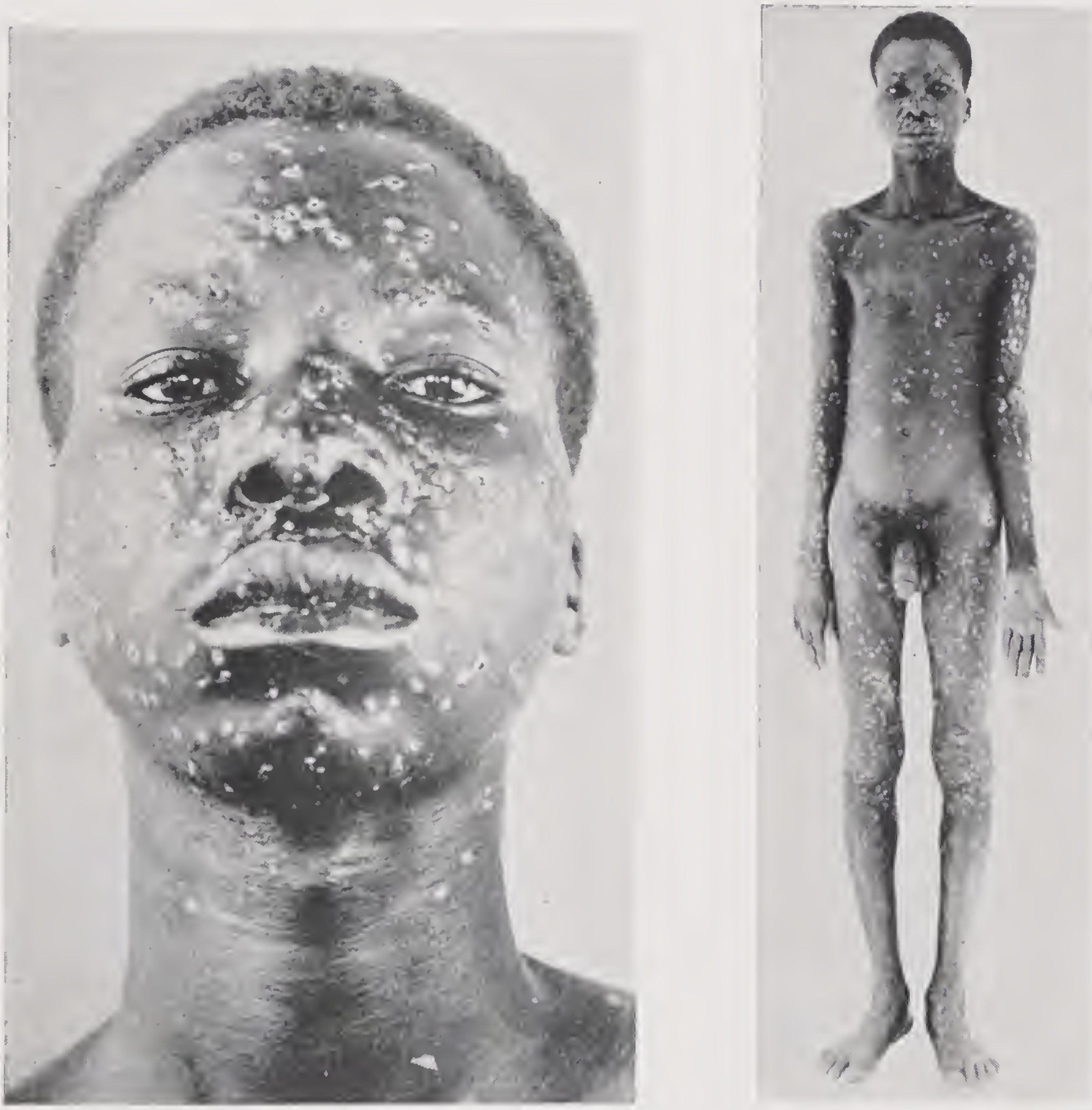

Fig. 1. Alastrim: Classic Eruption on the Face and Extremities
Phot. Tropical Institute, Antwerp

For vaccination, either glycerinated lymph prepared in local institutes or, if the breeding of cattle is difficult, dried vaccine may be used. The latter preserves its full activity, and may be made up into a suspension just before use. It has been said, without definite proof, that natural or artificial immunity to this disease may not last so long in the tropics. There may be several varieties of the virus, antigenically separable, as well for alastrim as for smallpox.

(B) CHICKEN POX (VARICELLA, WINDPOKEN)

Chicken pox has become world-wide in its distribution, even including the tiny islands of the Pacific Ocean. In Congo it has been known for several decades, but in 1911 it attacked the adult population in particular, which seemed to indicate that it was of recent introduction. However, it was benign and very much of the ordinary type. On the other hand, in 1887 the Marshall Islands in the Pacific had a murderous outbreak, doubtless the first invasion of the disease in this region.

Chicken pox is distinguished from Variola minor by the form of the temperature curve, the more superficial character and lack of suppuration of vesicles, which go on to form scabs, and also by the presence in the same region of the body of different aged lesions (i.e., vesicles and scabs).

Shingles (*Zona, Herpes Zoster*). This condition, once related to chicken pox, is also found in warm countries, the Pacific included. In Congo it is rare among the natives.

(C) MEASLES (ROUGEOLE, MASERN)

This condition is also world-wide. In Congo, where it was introduced some years ago, it is generally benign. However, on the Katanga plateau there have been a number of deaths (7–13 per cent) from respiratory complications, encephalitis and noma. There have also been numerous cases of conjunctivitis and keratitis, related with a vitamin A deficiency.

Historically the first invasion by the disease was catastrophic (Faroe Islands in 1781 and 1846 and Fiji Islands in 1874). However, in Fiji it was associated with dysentery and famine. There was also a serious epidemic in the New Hebrides in 1861. Recently there have been epidemics, sometimes of a serious nature, in the Pacific (Tonga, Cook) although the natives appear to be progressively increasing their immunity.

The symptomatology shows no definite difference from the usual course of the disease. The eruption is often somewhat papulous and is visible on the dark skin of the Negro.

German Measles (*Rubeola, Röteln*). This disease also exists in the tropics and in the small islands of the Pacific.

(D) MUMPS (OREILLONS, PAROTIDITIS EPIDEMICA)

Mumps is met with almost universally and does not show any definite differences in the tropics. However, it has not been observed in Malaya. There is also in Africa (Kwango, Belgian Congo) a parotid hypertrophy of chronic type, not congenital, of which the etiology is unknown. This condition has also been observed in Egypt and Madagascar.

(E) INFLUENZA (GRIPPE, INFLUENZA)

It is well known that the great pandemic of 1918 extended its ravages to the greater part of the tropical world without assuming at all the mild form which it showed at the time of its first outbreak in the spring of that year in Southern Europe (Spanish influenza, "Flu"). The mortality in countries such as India, Samoa, Tahiti, and the Congo was considerable, mostly from respiratory complications. In addition, small seasonal epidemics, between those of greater proportion, have been described, often introduced by ships coming from Europe. This latter fact has been demonstrated not only in the Congo and the Pacific, but even in Greenland. Almost always, unfortunately, there has been no bacteriologic information available concerning these epidemics. In 1940–1941, the epidemic in the Hawaiis was proved to be due to the Type "A" virus.

The diagnosis of influenza is difficult, and the practitioner in temperate climates has the same tendency of using and abusing the term as does his colleague in the tropics with the clinical diagnosis of malaria. In warm climates it is easy to confuse influenza with dengue fever although the latter does not show the same respiratory complications.

(F) RABIES (RAGE, LYSSA, TOLLWUT)

This cosmopolitan disease has been encountered in many tropical regions. The dog is the principal source of infection. In tropical America, rabies in man and cattle has been shown to be transmitted by the bite of the vampire bat, *Desmodus rotundus*. In Africa it has been stated that rabies occur in a milder form. This view is no longer justified.

In order to permit a precise diagnosis, it is necessary: (1) to keep the suspected dog under observation. If rabid, it will die within five days; (2) when the animal dies, to send the head and neck, packed in ice, to the nearest laboratory. If the delivery cannot be promptly achieved, one should remove the brain and place it in sterilized 50 per cent glycerine.

2. GENERAL INFECTIONS BY BACTERIA (PROBABLE)

(A) SCARLET FEVER (SCARLATINE, SCARLACH)

This malady is presumed to be rare and of a mild kind with most colored races, even in countries of temperate climate (Negroes of the

U.S.A.). In Europe it is, generally speaking, more serious with Northern and North Slavonic peoples than with those of the Mediterranean area. In fact, there is a tendency toward a mild type everywhere. Most observers in the tropics hold the opinion that it is not met with at all in these areas, unless perhaps among Europeans or Chinese (South China, India, Indonesia, Siam, Samoa, Puerto Rico, Tropical America). Yet it is supposed to have been observed in Guam, New Caledonia, Nauru, Fiji and the Hawaiis, but the race of the patients is not known to us. In the Congo it was seen only among Europeans. As a whole the disease seems more uncommon in all tropical countries than in temperate ones.

(B) RHEUMATIC FEVER (POLYARTHRITIS ACUTA, RHUMATISME ARTICULAIRE AIGU, GELENKRHEUMATISMUS)

Acute rheumatism (a resolutive and fugacious polyarthritis with tendency toward endocarditis, probably influenced by streptococci and their toxins) seems rare in the tropics. Exceptional in Calcutta (Rogers), it is supposed to be found only occasionally elsewhere in India. Extremely rare in Indonesia, it is said to exist in the Pacific, also among Australian natives (Northern Australia) and quite common in Brazil. In central Africa it is of rare occurrence. Williams admits its existence in Uganda, basing his statement on mitral stenosis, the practically constant rheumatismal etiology of which is well known. According to Suarez (Puerto Rico, 1945), cardiac localization is more frequent than arthritis. Chesterman came across it in Congo but rarely. It is probable that in many cases all sorts of articular diseases are mixed up. In India, MacKinley quotes 276,611 and Simmons and colleagues 598,000 (1937), while in the Belgian Congo 108,000 cases of acute rheumatism are mentioned in official reports of 1925 to 1938.

(C) ERYSIPELAS (ERYSIPELE, WUNDERS)

The disease seems to us very rare in central Africa. Yet in 1938, 59 cases and 2 deaths were quoted in the Congo among the natives, but one wonders if the streptococcic etiology was proved in all cases. Erysipelas exists in the Pacific, in central America, in the Philippines. It must be distinguished from filarian lymphangitis.

(D) DIPHTHERIA (DIPHTERIE, DIPHTERIE)

We consider this disease as belonging to the group of general infections on account of the toxic syndrome. It seems to be spreading gradually through the warm countries, although remaining rather a European sickness. In the Congo it is practically absent among the natives, but seen here and there among the Europeans and the natives associated with them.

Unmistakable strains have been isolated. Worthy of notice is the fact that most of the adult Congo natives have a negative Schick test and a corresponding antitoxic power in their serum. If, as Ramon states, "natural antitoxic immunity takes its origin in the specific infection, apparent or occult," the reality of this occult infection remains to be established among the Congo natives who seldom come into contact with Europeans. The disease also seems rare in other parts of central Africa, but is met in the Far East (Siam, the Malay Peninsula, Indonesia) and the Pacific area. In the Fijis native carriers of the disease seem to be common with few authentic cases. In the Hawaiis, the type intermedius is predominant. Diphtheria has been encountered fairly frequently among the armed forces operating in the Solomon Islands. Circumstances of war and the apparent mildness explain the relative frequency of paralysis (13 out of 18 cases observed by Norris, 1944).

Anthrax (Charbon bactéridien, Milzbrand): It is observed in various tropical countries including central Africa (Congo and Ruanda-Urundi), the Pacific, etc.

Glanders (Morve, Rotz): Also noted throughout the whole tropical area. In the Philippines it is said to be especially acute. The differential diagnosis is made with melioidosis (see Chapter IV).

(E) TYPHOID FEVER (FIEVRE TYPHOIDE, UNTERLEIBSTYPHUS)

The diseases discussed here are common or fairly common in most of the warm countries, especially in the densely populated ones and where hygiene is neglected (parts of Asia, India, China). Very primitive natives, living widely dispersed, seem to suffer little from this infection. On the other hand, knowledge of these countries is very fragmentary. In the Congo the disease has been mostly seen in industrial centers. Europeans are certainly exposed, but vaccination and better hygiene protect them more or less. It is said that with the natives, particularly in the Congo, the evolution is much shorter, the fever more oscillating, the stupor less intense. Perhaps it is necessary to remember that as a matter of fact a native will consult very late in an illness beginning progressively (ambulatory cases are fairly frequent).

Mouchet has shown us records of typhoid fever observed among the natives of Katanga, where the oscillating character was most decided and where the illness was of normal length (three to four weeks). The febrile oscillations went beyond two degrees centigrade and even fell below normal.

Paratyphoid A, the appearance of which resembles a mild form of typhoid, is seen more often in warm regions than in Europe. The bacillus was first isolated in Europe during the war of 1914–1918, but is seldom met in these days.

Paratyphoid B is sometimes a mild typhoid fever (Schottmüller's bacillus), at other times an alimentary toxic infection (the Breslau, Aertrycke, Typhimurium types) or else it is localized in the bladder or pulmonary organs.

Paratyphoid C appears in the Congo as a septic illness with pulmonary complications.

Group D includes the Eberth type and Enteritidis (Gärtner), agent of gastro-enteritis.

The diagnosis of these diseases must be made with certain forms of malaria (blood examination), epidemic or endemic typhus (more sudden), generalized tuberculosis, etc. Bacteriology (hemoculture, coproculture, the Widal reaction) is essential here.

Tetanus (Tetanos, Starrkrampf) has been reported throughout all tropical regions and presents no particularities. In the Congo, it is rare, considering the large number of ulcers and infected, badly dressed wounds.

3. DISEASES OF THE RESPIRATORY TRACT

In many of the warm countries, pneumonia, broncho-pneumonia and tuberculosis are among the principal causes of death. Several different causes, acting together, must be taken into account, and because these causes are, to a greater or less extent, common to both pneumonia and tuberculosis, both diseases are discussed together here, although they are naturally widely differing entities. They are taken up separately further on.

The predominant factor is an inadequate hygiene. In addition, a racial susceptibility has not been eliminated, and the sensitivity of the Negro to diseases of the lung and to tuberculosis is striking even in the U.S.A. But many other colored races are equally susceptible, and this fact tends to place the emphasis on hygiene. Overcrowding is the rule among the primitive natives, especially during the night. Clothing is either insufficient or worn uselessly during the warm part of the day. In infancy it is always rudimentary, or even nonexistent. A dietetic regime poor in proteins and vitamins has also been incriminated, and must be taken into account. The process of adaptation to industrial work is often accompanied by a heavy mortality due to these diseases.

In the Congo in 1938 affections of the respiratory tract represented about 15 per cent of all cases, and 25 per cent of the deaths. In Indo-China (1936), 2,508 cases of pneumonia were admitted to hospital, with 972 deaths. The index for the deaths from tuberculosis in Haifong (1937) was 263 per 100,000. In India in 1938, respiratory diseases caused 536,647 deaths, of which half were due to pneumonia. Tuberculosis reached the figure of 884,000 deaths, including 20 per cent of the "fevers" and 20 per cent of the lung diseases. The death rate for tuberculosis was about 5 times that in the U.S.A. (or 253 instead of 44.6 per 100,000.)* The same facts have been noted, but less definitely in China. In the islands of the Pacific, tuberculosis is also very widespread, being an important cause of death on Guam, the Solomons, New Caledonia, Tonga, etc. Pneumonia, too, is very common in these archipelagoes. In brief, these infections appear to be a predominant cause of morbidity and mortality for a very large number of natives in the tropics. On the other hand, European immigrants are less affected than in Europe.

The introduction of the sulphonamides has greatly reduced the mortality from pneumonia. In the Congo the fall is from 15–20 per cent to 2–3 per cent. Tuberculosis remains, as heretofore, the major problem.

(A) ACUTE INFECTIONS OF THE LUNGS

From time to time lobar pneumonia predominates, sometimes bronchopneumonia. Just as in Europe, the former is a primary infection, the latter often secondary to measles, whooping cough, and bronchitis. The symptomatology has not been observed to be different to an appreciable degree from that in temperate countries. The gravity of lobar pneumonia in many countries is strikingly apparent. In the Congo, before the advent of modern treatment, the average mortality was about 20 per cent even among robust young adults. Numerous complications explain this serious figure, for example, meningitis, pericarditis, acute malignant endocarditis, lung abscess, jaundice, and pleurisy (rarely exudative). The frequency of jaundice among the Negroes is striking, even in the U.S.A.

Among the broncho-pneumonias, atypical forms have been observed, chiefly in children. In these cases, ascaridiasis should be considered. An examination of the stool must always be made, and the appropriate treatment prescribed (oil of chenopodium, santonin, hexylresorcinol).

Whooping cough (Coqueluche, Keuchhusten). This disease is world-wide in its distribution, including the islands of the Pacific, and central Africa. It does not present any particular differences in the tropics.

Acute rhinitis (the common cold, Coryza, Schnupfen). This is also found almost everywhere, and appears to produce epidemics, leading to various pulmonary complications. It has been remarked that this infection is more important from a hygienic point of view than is commonly thought. Europeans are relatively free from attacks. Norris (1944) reports the interesting observation of an American ship calling with an apparently healthy crew in some small islands of the Pacific, the inhabitants of which did not suffer from common cold. An epidemic of the disease broke out among the natives and spread later on to the crew, almost duplicating the classic experiments on epidemiology made on mice by Topley and co-workers.

Spirochetal bronchitis. This is a subacute bronchial infection, often with blood-stained sputum, and various complications. The abundance of spirochetes is characteristic, and indicates a course of treatment with the arsenical specific. The action of penicillin at this writing had not been accurately determined.

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*It is probable that these figures, taken from Simmons et al., were collected in British India (three-fourths of the population of the peninsula). The latter country announced in 1935 a figure of 6,500,000 deaths from all causes.

(B) TUBERCULOSIS IN TROPICAL COUNTRIES

If one takes as an example a country opened up in relatively recent times to European civilization, the following facts can be established for the Congo:

1. Going back thirty or forty years, the true natives, with but little contact with the European, generally had a very low morbidity due to tuberculosis, and a very low index of positive tuberculin tests.

2. Tuberculosis is clearly European in origin, if one includes the possibility of Arab carriers, and as a rule the organism is of the human type. In the beginning, it was possible to trace the spread of tuberculosis from a European who had the disease. More recently, it has been the chief illness in the towns. Although unknown to the first observers (Mense, Broden) in Leopoldville, it was commented upon by Rodhain in 1907 and in 1911 it was one of the principal causes of death in this town. Out of 79 postmortem examinations, Mouchet noted tuberculous lesions in 36.7 per cent. The condition was not yet associated with a much higher morbidity rate, neither was there a raised figure for positive skin reactions (7 per cent among the adults of the town, absent in the surrounding tribe folk).

3. The progress of the cases in this period of extension was very rapid and the tendency to generalization of the disease was marked. Later the spread along the lines of communications and in the European settlements progressed quite rapidly. Tuberculosis was becoming an important problem. The morbidity grew continually, the mortality rate decreasing slightly. Not that the disease ceased to be fatal as a general rule, but its progress in the individual became slower. A growing rise in the index of positive skin tests was noted, and the final figures are nearly the same as those for the Europeans (Leopoldville, 40 per cent of adults in 1935). Finally, the native rural population was invaded, but relatively lightly. It seems that the scattered communities in the interior, with their isolated huts, and low population density, may be relatively unfavorable to the spread of the disease. Summing up, it is possible to see a period of introduction, then a first wave, notable not so much for the numbers of cases, but for their serious nature and their rapid progress. This was followed by a second wave more extensive, but in which the disease took on a more European form, although still very serious, the skin reaction showing a continuously increasing index. It has often been stated that the first wave was of the guinea pig type, or, in fact, a primary type of infection, clinically with frequency of generalized miliary forms and meningitis, even in adults, and of caseating visceral lesions, and rarity of surgical tubercu-

losis and sero-fibrinous pleurisy. It is interesting to note the statistics of Mouchet and Fornara, in the Congo towns between 1911 and 1925.

Total number of autopsies	129
Pulmonary lesions (50 per cent caseous pneumonias)	101
Generalized miliary tuberculosis	48
Tuberculous meningitis	7
Bone and joint lesions	5

In the following period of spread, it is less rare to see the disease take a relatively chronic course, and some cures have been reported. Nevertheless, the progress of the disease in the individual remains rapid, and the annual mortality rate for 1938 was about 30 per cent for the whole of the Congo. Similar observations have been reported from other countries. During the 1914–1918 war, Negro soldiers brought into France also showed the rapid types of the disease. Almost all the observers in the tropics, in the East as well as in Africa, emphasize the serious nature of tuberculosis in the colored races. The dry regions, of almost desert-like character, are attacked to a lesser degree.

It may be asked what explanation can be offered to account for the evolution of this disease, as it has been observed in the Congo. A *special racial sensitivity* is obviously possible. Actually the Negroes of the U.S.A., in spite of their adaptations to the climate and the mode of life, still have a tuberculous morbidity and mortality rate which is clearly greater than that of the whites. Tuberculosis is a disease in which care and early self discipline are required, and Negroes in general seem to have a more carefree psychologic attitude toward illness than whites. The characteristics of a race are as much psychologic as somatic.

General hygiene is of primary importance. In particular, negligence and overcrowding explain the ease with which massive contaminations may take place, while undernourishment explains the rapid course. An insufficient supply of animal proteins was obvious in Leopoldville between 1910 and 1915. This is a common occurrence in the tropics. An analogous aggravation of the progress of tuberculosis has been noted in Europe during the recent war (1939–1945).

Finally, many authors state that the diffusion of infection leads to the production of many cases of latent tuberculosis or discrete infections. The ultimate progress of these cases will always be more chronic, though not always favorable, if economic or social conditions or any other cause of debility should diminish the resistance (tuberculosis of the "reinfection" type). A raised index of positive skin tests in a section of the population would indicate a high number of cases of "premunition." In Norway (Heimbeck) and in the island of Bornholm (Madsen), the real protection afforded by latent infection with positive skin test has been clearly demonstrated. The experience in the Rand (South Africa) which showed a higher incidence of active tuberculosis among the recruits with positive skin tests does not contradict this point of view. It must be admitted that fatiguing and unaccustomed work had reactivated the latent tuberculous lesions more quickly in these people.

The social and individual prognosis of tuberculosis thus remains very serious in the tropics, and the fight against this disease is urgent and must be vigorously pursued. Inspections and early treatment, the isolation of open cases, advice on prophylactic measures such as the use of sputum pots and the provision of separate huts, as well as the isolation of healthy children from infected parents, must all be fully employed. Vaccination by means of the B.C.G. vaccine might prove a solution to the problem.

The diagnosis is normally only too easy when the native decides to come for advice. Wasting, fever, signs on auscultation, and a positive sputum may all be present. On the other hand, it is much more difficult to establish the diagnosis early in the disease, because of the lack of information of sufficient value on the part of the patient. In the Rand a systematic monthly weighing has been advised. The erythrocyte sedimentation rate is often abnormal in healthy natives, possibly on account of worm infections and malaria. Borrel has noted the presence of supraclavicular lymph nodes in 60 per cent of the cases.

Obviously radioscopy is capable of providing very inportant information and is becoming more and more frequently possible.

The differential diagnosis must sometimes take into account the other chronic diseases of the bronchi which may simulate to a greater or lesser extent the behavior of tuberculosis: pulmonary schistosomiasis, paragoniniasis, the pulmonary mycoses (see Chapter VI).

The various pneumoconioses, silicosis especially, are beginning to preoccupy the hygienists in charge of survey of industries in tropical countries. The experience gathered on the subject in temperate regions should be used in countries where industrialization is a recent phenomenon.

The other diseases of the respiratory tract are of less social importance. Laryngites are rare. When chronic, they are often due to syphilis or leprosy. The latter may give rise to acute stenosis of the larynx. The common form of acute bronchitis is frequently encountered, but the chronic form is rare.

Bronchial asthma is met with here and there among natives of various countries, and it seems to be quite frequent in the Far East. In Kivu (Congo), which is a region of high altitude, Europeans often develop asthma and accuse the dusts from volcanic eruptions. There is little to note concerning the pleura. Pulmonary adhesions are frequent in postmortem examinations of Congolese natives; pleural effusions are, on the other hand, relatively rare but arise from the same causes as in Europe. Carruthers (1947) has emphasized the frequency of pleuritis and pleurisy in the course of amebiasis.

(c) PRIMARY ATYPICAL PNEUMONIA

A number of years ago attention was drawn to a respiratory disease usually mild and appearing in small epidemics in different countries, including the tropics. The disease seems to be contagious.

Manifestations are characterized by moderate general symptoms: rather prolonged fever without initial chill, dry, painful cough with later ordinary sputum sometimes slightly blood stained. Stethoscopic examination gives little information: a few rales, rarely a certain degree of dullness and faded murmurs. On the other hand the x-rays show extensive infiltrations, and large peribronchial shadows, extending later into the parenchyma with slow resolution (preference for pulmonary bases). The blood shows little leucocytosis. Bacteriologic investigation remains negative. Cold isoagglutination in relation to O globules is frequent and well marked. The rare postmortems indicate at first an infiltration of the alveolar wall with round cells (typical for pneumonias due to viruses without superinfection), then bronchiolitis and a certain degree of alveolitis. Authentic foci of broncho-pneumonia may be seen (bacterial superinfection) and also atelectasis. The disease is mild but of rather slow resolution (average duration 10 to 14 days). Sulfonamides are inactive.

A certain number at least of these cases must be attributed to Q fever and to the viruses of influenza, ornithosis, lymphocytic benign meningitis, etc. In the majority of cases a special virus transmitted by coughing probably causes this condition as well as other mild respiratory syndromes.

Löffler's syndrome and tropical eosinophilia: The pulmonary involvement in both conditions is so striking that their description appears more logical in the group of respiratory diseases. The two syndromes have many common characteristics as is shown in the following chart. The former, however, was described in Europe, whereas it is said that the latter, considered as tropical, generally improves when the patient returns to temperate climates.

	Tropical Eosinophilia	*Löffler's Syndrome*
Distribution	Various races—tropical climates	Europeans—European climates
Symptoms	Pronounced: cough and asthmatiform attacks, sputum rich in eosinophiles, slight and short fever.	Mild, sometimes null (asthma absent) Fever Sometimes slight cough Slight sputum but with eosinophiles
	Irregular splenomegaly.	No splenomegaly
X-rays	Numerous small opaque foci, a few mm. in diameter	Transitory opacity (8–10 days), rather vague, fairly extended (several cm. without preference for apex). Unilateral or bilateral
Evolution	Chronic	Resolutive, rapid
Therapeutic	Neoarsphenamine, mapharsene, stovarsol, emetic	

	Tropical Eosinophilia	*Löffler's Syndrome*
Blood	Hyperleucocytosis (up to 70,000), marked eosinophilia (50–80 per cent)	Mild leucocytosis, at times marked eosinophilia (85 per cent); usual average 10–20 per cent
Pathology		Alveolitis foci with little fibrin and numerous eosinophiles
Etiology	Vague, possibly different on a parasitic basis (allergy) Strongyloids Filariae Schistosomes, etc.	Ascaris (evolution of larvae). Opacity appears 6–10 days after ingestion of eggs (Vogel and Minning, 1942) Other allergenes

4. DISEASES OF THE INTESTINAL TRACT

Intestinal disorders probably account for the greatest number of consultations in the tropics. For example, in Belgian Congo in 1938, 25 per cent of the patients were intestinal cases. The mortality among these was relatively slight, as many consultations were for benign diseases, e.g., slight helminthiasis, etc. In Gambia the number of "dysentery" cases comes close to the incidence of respiratory diseases. Congolese chiefs admit readily that their people die either of "pain in the side" (pneumonia) or of diarrhea (dysenteries).

The diseases which are more strictly tropical (dysenteries, helminthiases, cholera) are dealt with elsewhere. We shall consider only the cosmopolitan diseases here.

Stomatitis and gingivitis: A considerable amount of such infections are seen throughout all tropical climates. Apart from defective hygiene it is probable that avitaminoses play a role. In the Congo one notices nothing unusual from this point of view except the susceptibility of the Negro to bismuth and even more to mercury. Treatment with the latter, no matter how employed, is always very difficult to manage in Negroes, even in those possessing good teeth. Bismuth should also be carefully controlled. We make it a habit in all consultations for yaws and syphilis to examine the gums.

Noma is seen in cachectics (penicillin).

Dental caries: The incidence varies according to the race and probably to dietary habits. There is still interesting work to be done on this problem.

Parodontal diseases are moderately common, sometimes associated with pyorrhea, sometimes dry and expulsive.

Thrush is seen throughout the tropics.

Anginas: These are certainly not absent in the Congo, but are, nevertheless, considerably less common than in Europe. The Negro appears to be relatively slightly sensitive to the streptococcus, and diphtheria is practically nonexistent in the Congo.

Common sore throats are seen in the Pacific Islands and are almost certainly present in some degree everywhere.

Vincent's angina (associated with the presence together of spirochetes and fusiform bacilli) is reputed to occur especially in the tropics, along with gingivitis of similar etiology. This fact is not striking in the Congo.

Stomach: The simple dyspepsias appear to be more rare in primitive peoples than in civilized where the influence of psychic factors is well known.

Gastric ulcer is considerably less common in the tropics than in civilized countries, this being particularly true in the Congo. However, with the extension of surgery and also perhaps with changes of habits, more and more cases are being seen. At Hanoï, perforations constitute 5 per cent of abdominal emergencies. Duodenal ulcer, as in Europe, is stated generally as being more frequent.

Intestine: Appendicitis is also much rarer in the primitive people in spite of the frequence of helminthiasis. According to some surgeons appendicitis becomes relatively frequent among educated natives, whose way of living is more or less Europeanized. Schistosomiasis and amebiasis may be the origin of appendicitis here. Intestinal obstruction is met with from time to time. Strangulated hernia is very common. In the Congo, hernia, particularly inguinal, is of considerable social importance as a cause of morbidity and death. It is four times more frequent than in English military recruits. The reason for this frequency is not yet well known. It is probably related with abdominal dilatation in early age. Intestinal obstruction due to Ascaris is also worthy of mention.

5. LIVER DISEASES

Diseases of this organ are common in the tropics. The so-called "tropical liver," a rather ill-defined condition, will be dealt with elsewhere (see Chapter V).

Infectious hepatitis is encountered throughout the tropics. It varies in gravity, as probably also in etiology, though some cases are undoubtedly due to virus infection

Arsenical jaundice is quite common in primitive peoples particularly in the Congo. There is a strong possibility of the infection being introduced by the syringe. This raises the difficult question of the sterilization of syringes in these tropical dispensaries which are always so busy and crowded.* It is known that the infective agent in infective hepatitis is present in blood, witness the infection due to yellow fever vaccine to which human serum had been added as a protective.

Jaundice due to carbon tetrachloride is so frequent that in some countries the use of this product has been completely abandoned (Gambia, Congo).

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* Sterilization of syringes is far from easy in current practice, especially in the tropics. Ebullition in pure water (10 minutes); dry heat applied to cotton without singeing, at 140 C., for 45 minutes, guarantees at least disinfection, i.e., destruction of ordinary pathogenic germs. One can also have recourse to prolonged steeping, at least 15 minutes, in antiseptic solutions. Alcohol should only be used 70° plus formol (5 per cent) or a formol solution of 2.5 per cent plus phenol at 0.5 per cent plus sodium biborate at 1.5 per cent. It is useful to add to the above solutions 1.5 per cent of glycerin. After this chemical disinfection one must eliminate the antiseptic by rinsing in cooled boiled water.

As for perfect sterilization, i.e., bacteriologic, it requires an autoclave (120 C. for 20 minutes) or dry heat (160 C. for 45 minutes) and glass or very good quality metal syringes. At the dispensary we advise that syringes be left for some time in one of the above solutions, each time after its use or contact with blood. One must never use the same syringe for punctures and injections.

Cirrhosis of the liver: A number of observers have pointed out the frequency of liver cirrhosis among adults and children in tropical regions. Enlargement of the liver with ascites is also noted in children. This condition may disappear.

Experiments on rats and mice have shown that the lack of choline or of methionine (providers of CH_3 radicals) determines a chronic fatty degeneration of the liver, followed by portal cirrhosis. The lack of thioamino-acids (methionine, cystein) produces acute liver necrosis and consequently fibrosis and nodular hyperplasis. It is probable that an unbalanced diet, especially one deficient in proteins, intervenes in the so-called tropical liver cirrhoses. Fatty degeneration is part of the depigmentation-edema syndrome described in Africa (see Chapter VII).

The role of alcohol in the production of cirrhosis is possibly pro parte related with nutritional disorders. Schistosomiasis in the tropics is responsible for many cases of severe cirrhosis of the liver. The role of amebiasis (Rogers) has not been so well established. The prevalence of primary carcinoma of the liver which has been observed in the native populations of most tropical countries (Indonesia, Congo) seems frequently associated with previously existing cirrhotic changes.

Gall stones, on the contrary, are rare, especially clinically (Indonesia, Congo).

Hydatid cysts are occasionally seen in the tropics (Congo). South Africa is an important focus.

6. SPLEEN

A form of splenic abscess has been seen in Africa. Its etiology has been attributed to Spirachaeta duttoni or to Eberth's bacillus. Malarial splenomegaly sometimes gives rise to internal hemorrhage, usually as a result of traumatic rupture (3 per cent of abdominal emergencies in Tonkin).

7. CIRCULATORY SYSTEM

Diseases of this system are more rare in primitive peoples who have relatively short average longevity. In the Congo, during the year 1938, there were only 3,770 cases (255 deaths out of 1,298,405 patients treated). The fact that acute rheumatism is rare in most tropical countries probably partly explains this situation.

Syphilitic aortitis, aneurysms and obliterating arteritis are all encountered. Angina pectoris and hypertension are rare. Arteriosclerosis is common.

Varicose veins are extremely rare in Congo natives except in aged workers or soldiers. The affliction seems to be common in certain islands of Melanesia (Hyman, 1915).

8. URINARY SYSTEM

Nephritis: Acute or subacute nephritis is often reported. In Uganda medical reports show the presence of albuminuria in 16 per cent of cases, eventually with cylinders. This proportion rises to 36 per cent in subjects suffering from acute pulmonary disease.

The arteriosclerotic kidney appears to be rare, but most autopsies are made on young subjects. According to Vint, the Negro of Kenya suffers considerably from renal disease. At Batavia the same situation is noted. The average daily volume of urine of the Javanese is 900 cc. per day. In the Congo sulfapyridine readily provokes hematuria and anuria.

Renal lithiasis: Rare in certain tropical countries such as the Congo, it is very common in Indonesia and India. Vesical lithiasis is fairly common. Nephretic colics, hematuria, calculi have been attributed to dehydration in various warm countries. In a tropical field hospital, an observer found similar cases in 6 per cent of the nontraumatic surgical patients. As the new settler makes progress in his acclimatization, he has a tendency to drink less and he concentrates his urine. Treatment consists in a sufficient intake of beverage and of alkalizers or acidifiers according to the nature of the crystals.

Prostatic hypertrophy appears to be rare, or, more probably, subclinical.

9. ENDOCRINE SYSTEM

Goiter is seen in many tropical countries. A huge central African endemic area is noted, including the Congo (Ubangi) and French Equatorial Africa. The etiology is probably dietary. In contradiction to previous statements, toxic and thyroprival accidents have been observed. Iodized salt gave favorable results in Katanga.

The endocrine pathology in the tropics has so far been little explored.

10. METABOLISM

Diabetes is not common except in well-to-do people, whether Chinese, Indians or Europeans; it is very rare in primitive people who, by necessity, live frugally. Diabetes has, however, been found even in the Congo. The same may be said for obesity whether exogene or endogene.

11. LOCOMOTOR SYSTEM

The pathology of this system has not been sufficiently studied in the tropics to make more than general observations. If one is to judge by the Congo, however, its importance cannot be underestimated: between 1925 and 1938, there were, among government services, 108,000 acute cases and 273,000 chronic cases of "rheumatism." The natives themselves usually blame a previous infection of syphilis or yaws, and treatment of these is sometimes useful.

12. BLOOD DISEASES

Pathologic conditions of the blood and hemapoietic tissues have been noted throughout the tropical regions. The apparent rarity of certain hematologic diseases in these countries is probably more the result of a lack of information than a matter of fact. Anemia, or, more correctly, oligocythemia is frequently encountered in the tropics. In this condition, however, the hematologic pathology is different in the native populations than in the foreign residents. Thus, pernicious anemia has never been seen in the Javanese (de Langen and Lichtenstein) in the course of twenty years of continuous research, while it is not at all rare in the European and Chinese inhabitants of the island. In Africa, also, pernicious anemia appears to spare the black races except in certain districts where it has been discovered (Lake Tanganyika). Sprue, also, with its macrocytic blood picture, is not encountered in the tropics except in foreign residents. On the other hand, the macrocytic anemia known as tropical anemia has been noted in all the native populations of India, the Far East and Africa. This disease can scarcely be distinguished from the macrocytic anemia of deficiency, which is linked up with a diet deficient in proteins and rich in carbohydrates and vitamins. Clinically, however, it is not accompanied by gastrointestinal upsets and achlorhydria is rare. Edema is common in severe cases and glossitis is also found fairly often. Liver extracts and vitamins, particularly the B complex given parenterally, improve and cure the condition. Folic acid has proved to be especially active.

Several authors have drawn attention to the fact that the natives of East Africa and the Congo show a mean erythrocytic diameter superior to that of Europeans. It is wiser, however, not to draw the definite conclusion that this is a racial characteristic, as the native of the tropics cannot be considered as hematologically normal in view both of his diet, so frequently deficient, and of his numerous intestinal parasites.

A hereditary and familial condition of chronic, hemolytic anemia known as *"sickle cell anemia"* (sometimes referred to as drepanocytic anemia) has been found almost exclusively in the Negro race and was first described in North America. "Sickling" occurs often in the blood of healthy Negroes. The "sickle cell trait" was found in 7.3 per cent of a series of 8,453 Negroes. It seems that only 1 out of 40 Negroes, whose red cells sickle, show the classic signs of sickle cell anemia: low red cell count, jaundice, bone deformities and the peculiar elongation of the red cells in sealed preparations where the sickling is at a maximal rate in from two to six hours after the blood is drawn. Sickling conditions of the blood have recently been encountered in seven white families (six of which were of Greek and Italian stock) and also in Mexicans. Isolated cases have been found on the Gold Coast of Africa, in Algeria, in Peru and Cuba.

Murray-Lyons (1944), Robertson and Findlay (1947) have emphasized the frequency of the sickle cell trait in West Africa (20 per cent) with the following pathologic consequences: hemolytic anemia, hemoglobinuria, thromboses and infarcti, pains in the joints, abdomen and spleen, cerebral symptoms, death of the fetus or the new born.

It also appears that the blood of the Congo natives shows a greater ovalocytosis (Günther's eccentricity coefficient).

In any case it is always more difficult to interpret the significance of hematologic modifications in tropical regions than in temperate climates. In the tropics erythropoiesis is affected indirectly by intestinal affections. The leucocytic cells are probably directly affected by certain parasitic protozoa of the blood. An intense and absolute neutropenia giving a differential count with a predominance of lymphocytes is characteristic of infections by Plasmodia, Trypanosomes and Leishmania. The histocytic system is also stimulated in these infections. The macrophages of the bone marrow are more active and monocytes increase in number in the peripheral blood. Monocytes, and less frequently neutrophilic granulocytes, sometimes show granules of malarial pigment in their cytoplasm. Finally, eosinophilia is so characteristic of helminthic infection that it constitutes the first sign, particularly of filariasis. Tropical eosinophilia has already been dealt with in this chapter in the section on Diseases of the Respiraory Tract.

The differential diagnosis of the hemoglobinurias will be dealt with in the consideration of Blackwater fever which is the commonest tropical form (see Chapter IV).

The examination of the bone marrow after a puncture of a flat bone can provide important clues in confirming or establishing the diagnosis and prognosis of most hematologic diseases. The myelogram should be made on 500 cells, counting these on the medium zone of the smear from one edge to the other (see Appendix C).

The modifications of the bone marrow due to diseases of warm climates have not been investigated systematically. With the exception of *Leishmania donovani* in kala azar and, to a certain extent, of *Plasmodiums*, the hematotropic parasites are no more easily found in the bone marrow than in the blood.

For the doctor practicing among natives with limited education, the puncture of the crista iliaca recently advocated for the bone marrow biopsy (van den Berghe) is particularly indicated. This procedure is less painful than the sternal puncture, thus having definite psychologic values for the patient, and it can be repeated almost indefinitely at short intervals.

13. NEUROPSYCHIATRIC CONDITIONS

Infectious diseases are often the cause of disturbances of the neuropsychic system.

Cerebrospinal meningitis: In Europe and the United States of America, this disease is often hibernal. It has, nevertheless, created serious epidemics in the tropics. The dry season (cold and dusty) is particularly dangerous in Central Africa. No deviation from the ordinary course of the disease is to be noted except its gravity.

Infantile paralysis: A summer disease, occurring in temperate countries, it has also been observed in the tropics, especially the Congo.

Epidemic encephalitis: It is observed in the tropics.

Syphilis: Meningovascular lesions are fairly common (hemiplegiaparaplegia). Tabes appears much more rarely, especially in the Congo. General paralysis is observed more and more in various half-primitive peoples.

Chorea seems rare (relation with rheumatism).

Epilepsy is fairly common. *Migraine* headache seems nonexistent in the Congo. *Hysteria*, on the other hand, is common, and such *mental troubles* as amok, latah and koro, described in the Far East, are dealt with in the following section. Most European psychoses are to be found in Africa or in Asia. Infectious confusions, epileptic psychosis, trypanosomiasis psychosis are frequent. Schizophrenia appears to follow in the course of civilization. Affective psychoses (melancholia-mania) would appear to be less frequent than in Europe.

14. EXOTIC PSYCHOPATHIAS

Amok: This disorder, especially met with among Malayans, is an attack of psychomotor excitement with murderous tendencies. It is manifested by a homicidal running wild, with sundry victims, until the madman is mastered or killed. Sometimes, the maniac attacks animals. Amok may be caused by infection (malaria, etc.) but may also be of purely psychic origin, an amnesia for the period following in the wake of the attack. It seems that there is at the base of amok a kind of traditional ritual, a manner of expressing overly vivid emotions, or of settling overly painful internal conflicts.

Latah: This mental disturbance is also seen among Malayans. It is characterized by a certain degree of confusion, echolalia or echophraxia. The attack follows a fright or sudden excitation. It is, in fact, a state very similar to hypnosis. Experienced observers do not, however, connect it with hysteria.

Banga: Attacks of wandering, probably hysterical, met with among riverine populations of Lower Uele (Mobenge in particular).

Koro: Anxiety neurosis, which attacks the Chinese and certain other Asiatic peoples (Celebes, Borneo). The subject fears the disappearance of his penis and fixes it vigorously either by hand or by attaching it to some object. The attacks recur fairly frequently.

15. TUMORS

There is hardly a type of tumor, benign or malignant, which has not been met with in the tropics. Uterine fibromyoma and lipomas are common. Among cancers, certain forms appear to be rare, gastric epithelioma, for instance. Others are frequent: primary carcinoma of the liver, melanomes. Oral cancer is frequent among betel eaters (India, Ceylon). Malignant growths of the neck are relatively common in Indonesia and Indo-China.

Cutaneous epitheliomas are rare in the Congo. Spinocellular forms are rather common in other countries. In Nigeria, however, malignant transformations of long standing tropical ulcers have been observed. In Indonesia, cutaneous cancers of the leg and foot would appear also fairly common. Cancer of the penis is frequent in Indo-China among the uncircumcised. The "Kangri Cancer" of Himalayan regions is well known: chronic burn by the "Kangri," or warming pan, becomes malignant. The proportion of sarcomas to epitheliomas is greater in the tropics than in Europe.

16. SPECIALTIES

Among these, many need little consideration here: gynecology and obstetrics, lower urology (great frequence of blennorrhagia), auricular affections.*

In the section dealing with ocular disorders, one also considers the importance of trachoma in various hot and dusty countries (North Africa, Southwestern United States, Katanga). Alimentary deficiencies are also a factor. Ocular onchoserciasis and lack of vitamin A (see Chapter VIII) are dealt with further on.

Dermatology has a very important place in the tropics. Certain affections are more particularly tropical and will be discussed later. Others, cosmopolitan in character, are especially frequent but need not be described here: leucodermia, albinism, sarcoptic itch, divers prurigos, syphilis, pyodermitis (recurrent furunculosis appears to be rare among Congo natives), mycoses, chancres. Finally, certain skin diseases are rare or absent in primitive peoples: noninfectious eczema, psoriasis, erythematous lupus, tuberculides, sarcoids, lupus (absent in the Congo and in Indo-China according to Montel), alopecia, baldness (appearing late in the Congo and Indo-China). One should also add those diseases where cold is a determining factor: chilblains, indurated erythema, sub-malleolary erythrocyanosis, livedo, acro-asphyxia (Montel). Varicose eczema and varicose veins are rare.

According to Montel the syndrome of nodular erythema in Cochin-China seems often to be related with ascaridiasis and would respond favorably to the treatment of this helminthiasis.

Recent studies have shown the part played by avitaminosis and malnutrition in many dermatologic syndromes seen quite frequently in tropical countries (see Chapter VIII).

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* According to Havard (verbal communication) otitis plays a decided role at Elisabethville among black young infants: 212 otitis cases in 702 cases of general diseases.

Chapter IV

GENERAL INFECTIONS

1. AFRICAN TRYPANOSOMIASIS* (SLEEPING SICKNESS)

DEFINITION. Chronic infectious disease caused by *Trypanosoma gambiense* or *Trypanosoma rhodesiense*, transmitted by various tsetse flies (Glossina) and characterized by infectious phenomena usually followed by chronic meningoencephalitis with fatal conclusion.

HISTORY

An Arab chronicler of the fourteenth century refers to a Negro king who had succumbed to a sleeping sickness. Recent European sources present more authentic and detailed accounts. From 1721 to 1734, John Atkins, an English naval surgeon, described an affection from which Blacks on the Guinea Coast suffered, characterized by lethargy, dementia, and death. In 1803, Winterbottom made similar observations in Benin Bay (Nigeria) and especially pointed out the lymph gland hypertrophy well known to slave dealers (Winterbottom's sign). Since 1808, the disease has been observed in the French West Indies; Guerin, in 1869, in defense of a thesis at Paris, collected 148 observations made on natives of the Congo, at Martinique. At the end of the nineteenth century, European penetration into Central Africa gave increased interest to sleeping sickness. Mense, in 1885–1887, characterized it as endemic in the Lower Congo. Belgian missionaries also have noted it in their reports. At the mouth of the Kasai, at Berghe Sainte Marie, a serious epidemic raged from 1893 to 1900. This situation aroused interest in Belgian Colonial spheres, and gave birth to the Leopoldville Laboratory, dating from 1899. In 1899–1900, another epidemic broke out at Lake Victoria, possibly brought from the Congo by Stanley's troops marching to the assistance of Emin Pacha.

Even in Europe, clinical and anatomic observations were made on sick Blacks brought back from Africa to London or Paris. At that time, the disease was thought to attack only Blacks, which explains why cases of white Belgians under observation in Brussels were, at the end of the nineteenth century, diagnosed only retrospectively. The first European case which was well described was that of Mrs. S., an English missionary established in the Belgian Congo, and published by Manson in 1902–1903 The etiology of the disease had just been brought to light at about this period (see further).

The therapeutic had preceded, of course, the precise scientific findings. From 1890 to 1895, Lingard and Bruce employed arsenic on animals and this element was also employed on man. Thomas (Liverpool) introduced atoxyl experimentally in 1905 and its use for human medication followed rapidly. Experiments with antimony were made on animals by Plinner and Thompson in 1907, and on man in the Congo by Broden and Rodhain in 1908.

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* X. Brumpt put forward the designation "ose" for all parasitic affections; this preferred designation is too rarely employed. "Trypanose," a term frequently used by French authors, is rather erroneous. The correct French terms are: Trypanosomose, Maladie du Sommeil. In German: Schlafkrankheit.

Erlich (1903–1915) inaugurated modern chemo-therapy by experimenting on the trypanosomiasis of the Muridae, discovering the arsenical compounds. In 1920, the Bayer 205 and the Tryparsamide were added to our therapeutic arsenal, and more recently, orsanine, while just before 1940, the quanidines and diamidines.

GEOGRAPHIC DISTRIBUTION

The extensional limit of *Tr. gambiense* corresponds to the distribution of *Glossina palpalis* and *Glossina tachinoides,* i.e., from Senegal to Benguela and from the coast as far as the upper course of the White Nile and Great Lakes (French East Africa, British West Africa, Cameroun, Spanish Guinea, French Equatorial Africa, Belgian Congo, Angola, South Anglo-Egyptian Sudan, West Uganda, and Tanganyka Territory).

The disease, however, does not exist at present in the whole of this area: in the Belgian Congo in particular, it is not found at an altitude exceeding 1200 meters (absence of *Gl. palpalis*) and it is not so common in the Congo central forest, except in the vicinity of streams and big rivers. It is necessary, in each country, to take into consideration the phytogeographic aspect and the corresponding spread of tsetses.

The distribution of *Tr. rhodesiense* is rather limited: North East Rhodesia, South Tanganyka Territory, Nyassaland, etc.

One should note that the disease has never become native in tropical America because of the absence of glossines.

ETIOLOGY

The trypanosomes of inferior vertebrates have been known since 1841,

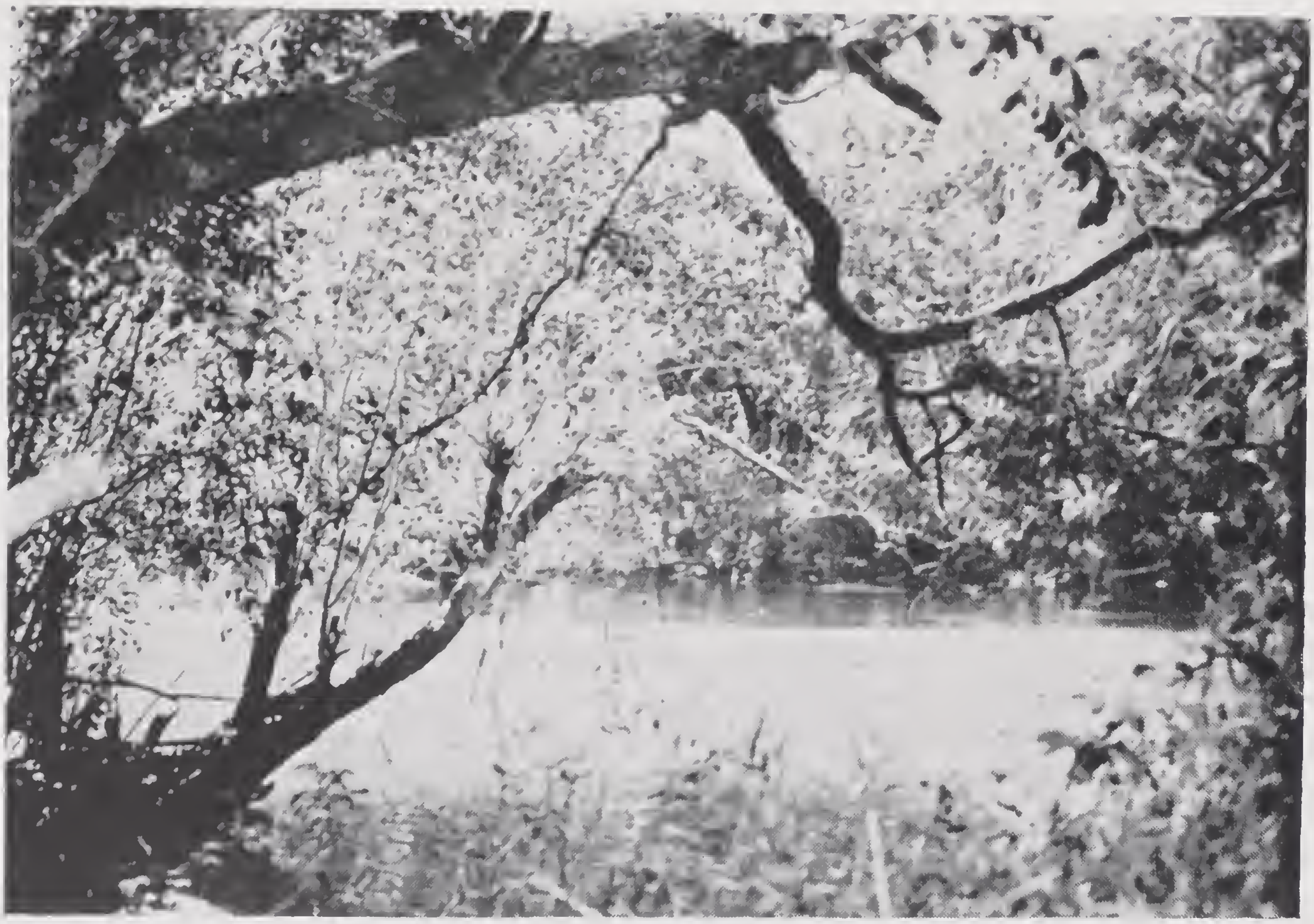

FIG. 2. CLASSIC SITE FOR GLOSSINA PALPALIS, CONGO
Phot. L. van den Berghe

those of mammalia since 1878 (Lewis, *Tr. lewisi,* trypanosome slightly pathogenic for rats) and 1880 (Evans, *Tr. evansi,* pathogenic trypanosome of horses, camels, etc.). In 1894, Bruce proved that nagana, a grave illness of horses and cattle in South Africa, is caused by a blood flagellate (*Tr. brucei*) transmitted by the tsetse fly, *Gl. morsitans.* In 1901, Forde discovered in the blood of a European suffering from intermittent fever at Bathurst (Gambia) mobile vermiculary parasites, which were recognized as *Tr. gambiense* by Dutton, who observed them in the same patient. Nevertheless, although the blood of natives showed the presence of the same parasites, its relation to sleeping sickness was not proved, the patient presenting none of the classic signs of this affection.

In 1903, at Lake Victoria, Castellani observed trypanosomes in the cerebrospinal fluid of 5 subjects suffering from sleeping sickness and named them *Tr. ugandense.* Bruce at once recognized the importance of this discovery, proving the presence of this parasite in 70 per cent of sleeping sickness subjects, and its absence in healthy subjects. Bruce and his colleagues established the identity of *Tr. gambiense* and *Tr. ugandense* and its transmission by another tsetse *Gl. palpalis.* The cycle of development in the fly was completely elucidated only by the work of Kleine and Taute (Tanganyka 1909–1911). In 1910, Stevens and Fantham described a new species of human parasite, *Tr. rhodesiense,* the transmission of

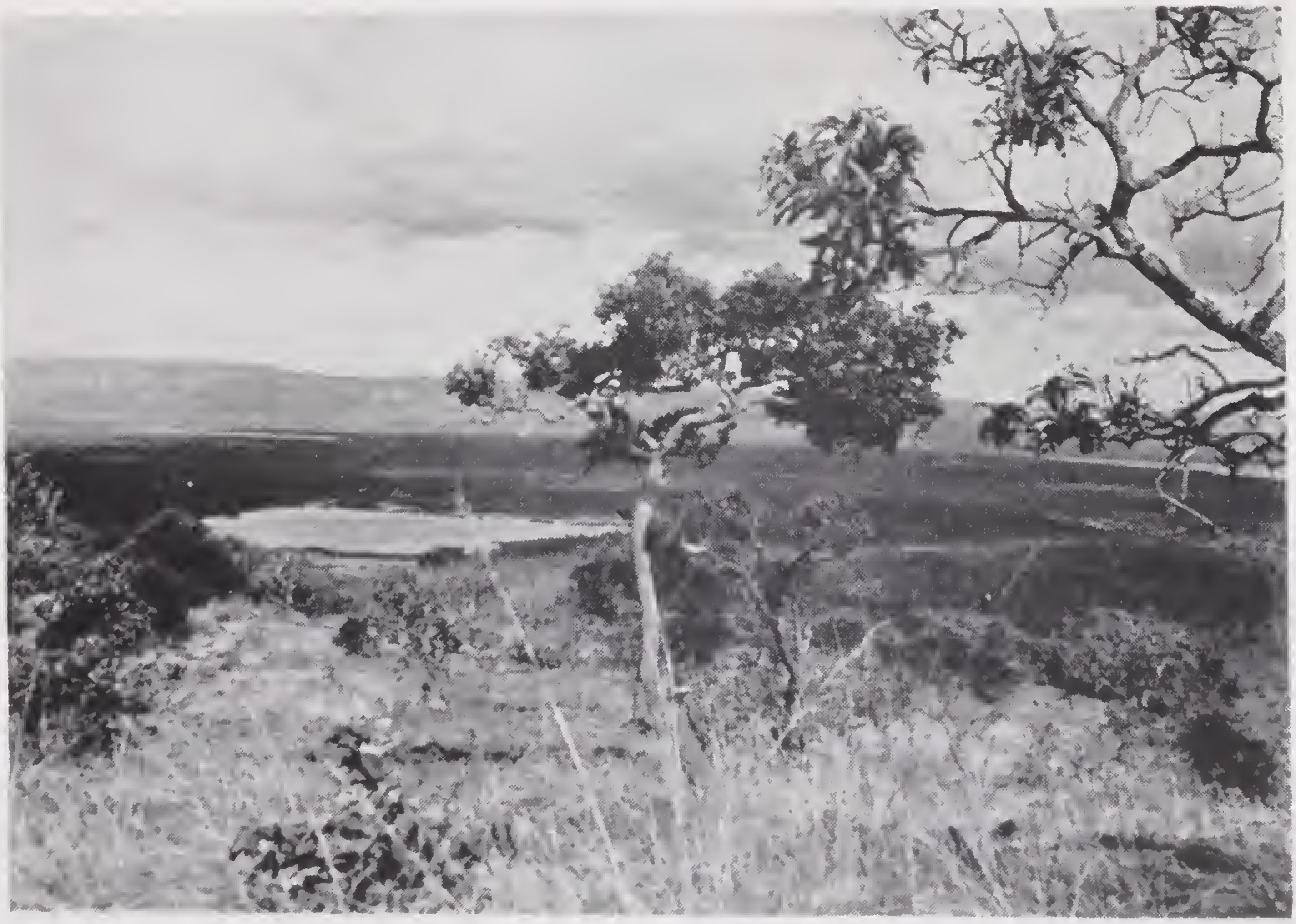

FIG. 3. CLASSIC SITE FOR GLOSSINA MORSITANS, CONGO
Phot. L. van den Berghe

which by *Gl. morsitans* was demonstrated by Kinghorn and Yorke in 1912.

Amid this vast group of trypanosomes with their morphologic differences, the three above-named species, i.e., *Tr. brucei, rhodesiense,* and *gambiense,* so greatly resemble one another that specialists now have a tendency to consider them of common origin, or varieties of the same parasite. They are mobile, elongated organisms in plasma, the morphology of which appears after Romanowski staining (see Appendix C). Their length varies from 10 to 30 microns. There is a long narrow type with a long free flagellum and an undulating lateral membrane, and a short broad type with undulant membrane and a mobile very short flagellum. With a pale blue cytoplasm, the oval central nucleus becomes violet-red upon staining. The posterior extremity shows a red poncti-formed, pin-point or bacilliform small organite, called kinetoplast. The flagellum, issue of this substance, projects itself forward while following the lateral undulating membrane thus prolonging it. The organism multiplies itself by longitudinal division.

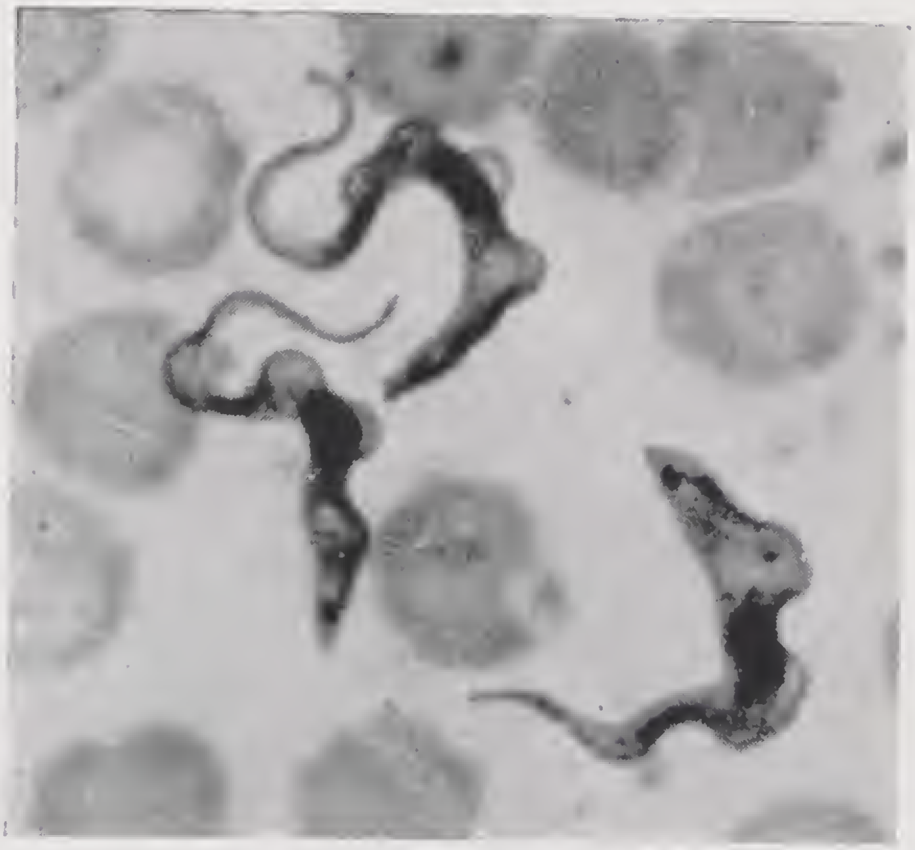

FIG. 4. TRYPANOSOMA GAMBIENSE. THE TWO FORMS, ELONGATED AND BROAD
Phot. Tropical Institute, Antwerp

Tr. brucei is considered as the original strain, and common among wild or domestic animals. Man appears to be nonreceptive. *Tr. rhodesiense* is of very close origin to *Tr. brucei*, transmitted by the same glossine but probably recently adapted to man who offers little or no resistance to this infection which is consequently acute. *Tr. gambiense* would finally appear to be a strain of long standing adaptation to *Gl. palpalis* and to man, with whom pathologic evolution is chronic. By experiment, these three varieties infect small laboratory animals and monkeys (except the genus *Papio*, and in a lesser degree *Cercocebus*). *Tr. rhodesiense* and *Tr. brucei* usually produce very acute infections, without trypanolytic crisis in mice and rats, acute infections often with lytic crises in guinea pigs, and subacute infections with important local lesions in rabbits. *Tr. gambiense* is usually much less virulent, the infections being of a more chronic type and sometimes with marked neurotropism.

The animal reservoir of virus is important with respect to *Tr. brucei* and *rhodesiense* (wild or domestic ungulates, without apparent signs of illness in the former). It is possible that in nature, domestic animals (pigs, dogs, etc.) may also serve as reservoirs for *Tr. gambiense,* and even wild animals (sitatunga antelope, *Limnotragus spekei*).

Epidemiologically, however, the real reservoir of *Tr. gambiense* is man. We have seen the disease circulate by following the channels of human penetration (trading, military expeditions, etc.). Inversely, the prophylactic schema put into practice, and essentially based on the therapeutic sterilization of the human reservoir, has proved very efficacious.

TRANSMISSION

Tr. gambiense has for its principal vector *Gl. palpalis. Gl. tachinoides* replacing the former in different parts of West Africa. *Tr. rhodesiense* has

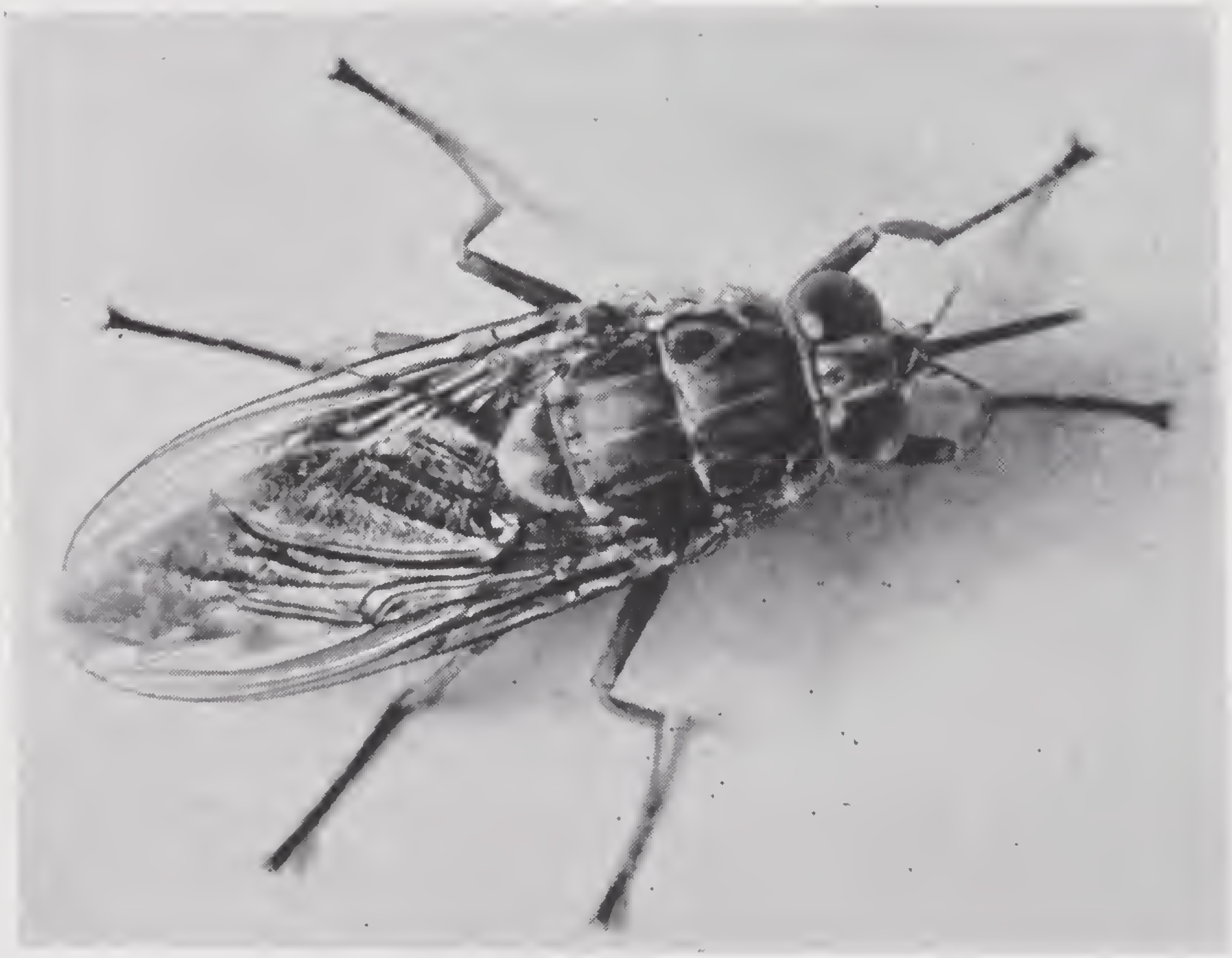

FIG. 5. GLOSSINA PALPALIS
Phot. Tropen Institut, Basel

for its principal carrier *Gl. morsitans*, also *Gl. swinnertoni* and *Gl. pallidipes*. The latter transmits *Tr. gambiense* in Uganda.

Gl. palpalis haunts the shady forest-clad river banks to a depth of about 25 meters. Shade and water are indispensable to *Gl. palpalis*, and the geographic distribution of this species is limited to forests and forest galleries in Central and West Africa (temperature 20–25 C., humidity 80–90 per cent). *Gl. tachinoides* is found in the river galleries of the pre-Sahara savannas.

Gl. morsitans, less hydrophilic, dwells chiefly in the wooded savannas of East and South Africa and often crosses over a kilometer of nonwooded space.

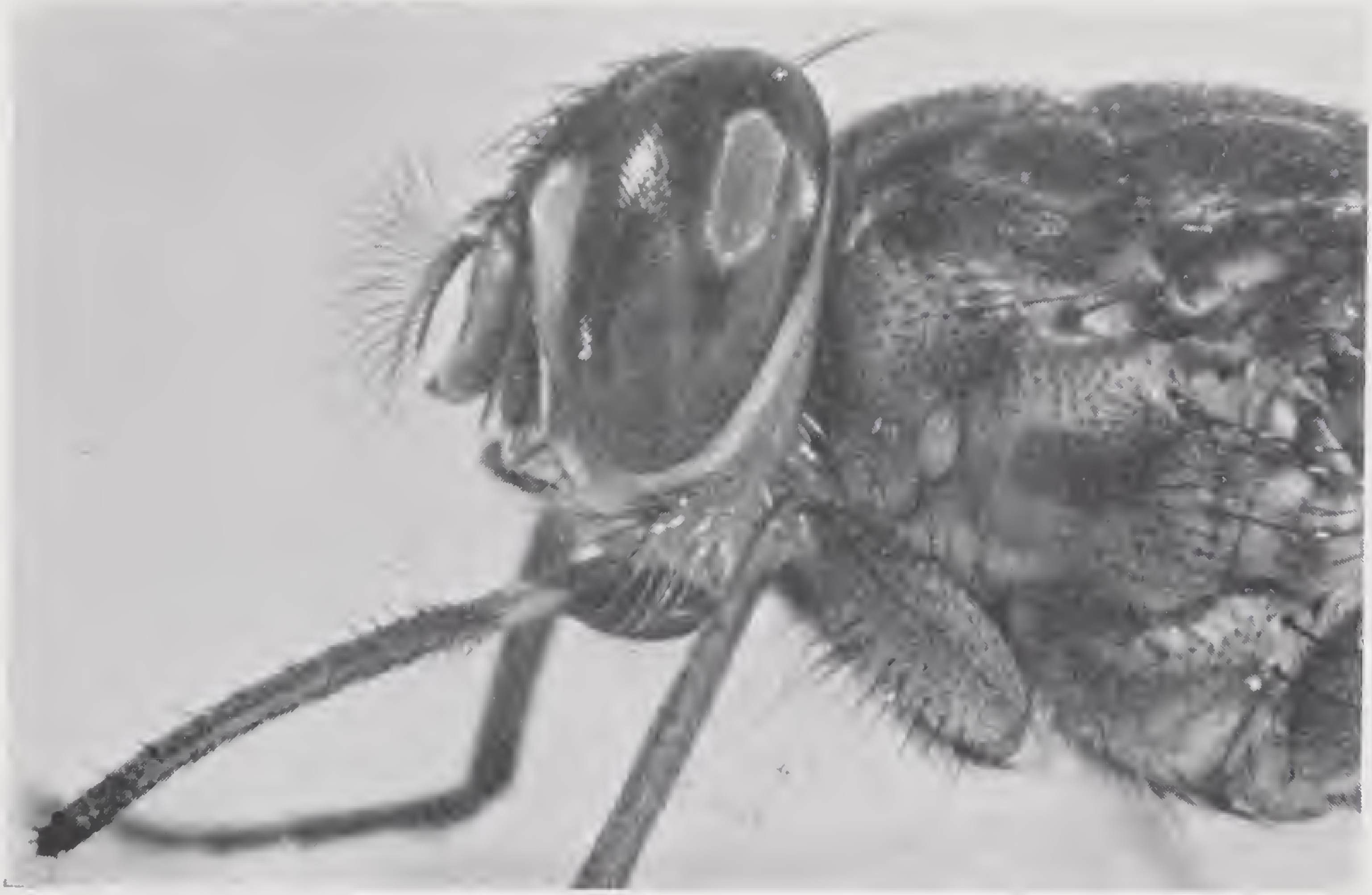

FIG. 6. GLOSSINA PALPALIS
Phot. Tropen Institut, Basel

The biologic cycle of trypanosomes is identical for the two types of fly. The flagellates ingested at the moment of the bite multiply themselves under various forms in the fly's intestine. Finally, they emigrate to the salivary glands where they take the infectious "metacyclic" form. According to the temperature and humidity, flies are infectious from 12 to 30 days and more after the infecting bite, and remain so for approximately 200 days, which means about their entire life span (4 to 8 months). The proportion of flies which become infectious after feeding on an infected subject is always low (2 to 10 per cent). Infection in flies is not hereditary. Females are viviparous and lay one single voluminous larva on dry and shady ground. The larva works a tunnel of about 5 centimeters in depth. Since gestation lasts ten days and the development of the pupa at least three weeks, the glossine reproductive capacity is rather limited. Male and female bite during the warm hours and can transmit the disease. Mechanical transmission is possible when tsetse or other biting flies (stomoxes) return to an accidentally interrupted meal, and pass from an infected to a healthy individual. It is possible that this fact may have an important significance in epidemic or epizootic cases.

The ecology of glossines, more especially that of *Gl. palpalis*, explains the danger of certain sites of economic importance situated in an infected zone while the village itself is well situated (cassava steepings, forests, streams, etc.). The disease is, therefore, often professional: woodcutters, fishermen. The glossine represents the essential element of transmission and in order to realize this it suffices to remember the example of tropical America, where in spite of the importation of infected Negroes, the hot climate, and various insects, sleeping sickness has failed to establish itself. Nevertheless, cases of transplacental transmission have been observed, notably that of a French woman returning from Africa and giving birth, at Marseilles, to an infected infant.

Koch, at one time, admitted the possibility of transmission during sexual intercourse. Although such a mode of infection is a general rule in cases of dourine (trypanosomiasis of horses), it has not been proved to be the case in human beings. A few rare laboratory infections have been noted.

IMMUNITY

Information on what happens to man, living in natural surroundings, is uncertain. With animals and with human beings, chemical therapeutic treatment leaves a brief immunity from the homonymous strain. Spontaneous recovery leaves a more or less solid immunity. With animals, one often observes a state of infection-immunity or premunition (according to Sergent). Possibly such a state in human beings is on the way to realization in certain countries. (See further, Prognosis.)

PATHOGENESIS

Highly acute infections of rats and mice with continued progression, apparently kill by metabolic complications, especially by glucose substraction (Dubois). Certainly the same cannot be said for the course of human infection, this being more discreet and interrupted by trypanolytic crises. But observation has taught that trypanosomes are parasites of intercellular space and because of this exercise inflammatory action (Morax, W. Yorke, Wolbach, etc.). More recent studies have confirmed and amplified these conceptions (Péruzzi, Regendanz and Höpli), demonstrating in animals the existence of myocarditis and pericarditis, inflammation of the plexus choroides, etc. As a matter of fact, the gravity of the disease of sleeping sickness, due to *Tr. gambiense* at least, is due to the development of nervous lesions. It may be that purely toxic mechanisms are at work in certain rapidly evolving forms, studied particularly in *Tr. rhodesiense*, or in any case, lesions of thoraco-abdominal viscera.

PATHOLOGY

Except for intercurrent malady, a fatal outcome is not to be expected in the primary stages. The main pathology is found in those who have had meningoencephalitis (*Tr. gambiense*). Various complications are frequent. Macroscopic examination is not of particular interest, but shows terminal emaciation with, in a few cases, persistence of hypertrophied lymph nodes. Splenomegaly is less important than in certain animal trypanosomiases. The opening of the skull shows profuse and sometimes slightly opalescent cerebrospinal fluid (real pus is a sign of additional infection). The meninges, especially the cortical ones, are edematized and congested. In subjects infected with *Tr. rhodesiense*, a gelatinous meningeal exudate has been encountered.

Autopsy of patients having died from *Tr. rhodesiense* infection sometimes shows lesions of the nervous system (treated cases), sometimes myocarditis, polyserositis, etc.

Animal experiments clearly demonstrate the opposition between nervous lesions on one hand (chronic infections) and myocardic and serous lesions (acute infections) on the other.

Histopathology is more instructive.

Skin. Erythematous spots show a perivascular infiltration with mononuclear cells.

Lymphatic ganglia show cellular proliferation and plasmocytosis in the lymphoid structures, with multiplication of endothelial cells. Erythrophagia is also to be noted. One can observe hemorrhages, cellular necrosis and subsequent fibrosis, which explains the tardy retrocession of adenitis.

Nervous system (particularly *Tr. gambiense* or treated cases of *Tr. rhodesiense*). This is a matter of diffuse meningoencephalitis with marked infiltration of both glial and mesenchymatous origin. Infiltration in the nervous tissue usually takes the aspect of perivascular cuffs (Virchov-Robin spaces) and is composed of plasmocytes, lymphocytes and Mott cells. Diffused infiltrations are to be seen in the meninges, the choroid plexus, and in the nervous tissue itself where the deep parts of the cortex as well as the white matter are especially involved. Glial reaction remains mild. Mott cells (morular cells) are of plasmocytic origin. These are large oval cells with an eccentric nucleus more or less pyknotic, the cytoplasm containing acidophilic transparent spheres. By disintegration, Mott cells transform into Russell corpuscles. Morular cells are to be found in infiltration, but they are especially dispersed in the nervous tissue. They pass into the cerebrospinal fluid where their presence is pathognomic, which is not the case in the tissues. One finds them also in the spleen, liver, etc.

The neurones are only slightly affected. Sometimes tumefaction with chromolysis can be seen; the myelin may also be altered.

The lesions resemble those of neurosyphilis, but the latter presents a more peripheric topography, more gliosis and lesions of the neurones.

As for the myocardium, an exudative myocarditis (especially in *Tr. rhodesiense*) is to be seen. Fibrous lesions have been attributed to the evolution of these infiltrations.

SYMPTOMATOLOGY

Incubation. Formerly it was estimated that incubation lasted for months or even years, but this was because the first stages passed unperceived. At present we know that incubation is roughly from five to twenty days (Corson's experience, and also former observations made by Broden, etc.).

Invasion. This may be accompanied by a primary lesion appearing at the site of the bite. It is an infiltrated erythematous zone, rather painful, and accompanied by a lymph ganglion reaction and, when disappearing, leaves hemorrhagic streaks. Corson regularly observed it in subjects experimentally infected with *Gl. morsitans* (*Tr. rhodesiense*). Duke noted it in less than one-third of his voluntary infected cases (17 in all). Sicé considers it a regular occurrence among Europeans. We have never encountered it among Negroes who possibly take no notice of it. The fact that trypanosomes appear in this skin lesion sooner than elsewhere and also its susceptibility to treatment would seem to give it the character of a primary lesion.

It is customary to divide the evolution of the disease into two periods; the first is the septicemic, hemolymphatic stage in which parasites are found in the blood and lymph; the secondary or nervous stage is that of meningoencephalitis.* A period of cachexia follows which authors have termed the tertiary stage.

1. *Septicemic stage.* This period shows rather insignificant infectious signs, the clinical diagnosis of which is often uncertain. *Fever* is usually the initial symptom. It presents, however, no special characteristic either in its curve or in the associated symptoms. Shivering and sudation are less pronounced than in malaria. Feverish attacks recur irregularly, are more frequent at the beginning of the illness, and are accompanied with various troubles which may persist during the intervals, such as asthenia, headache, insomnia, irritability. The fever is commonly of remittent type. It may be absent or pass unobserved by Europeans and more especially by Negroes.

The eruption (trypanid) is often observed among Europeans. It is shown most frequently by erythematous elements, fairly large, sometimes annular, rarely infiltrated, and usually nonpruriginous. The favorite seat of these troubles is the trunk. Time of appearance varies and is sometimes recurrent. With black subjects this symptom passes unobserved.

Tachycardia with hypotension as warning of myocardic trouble is frequent. It can be observed between attacks of fever, and because of this acquires great value in diagnosis. (We have, however, seen it diagnosed as pure cardiopathy.)

Finally, the most important sign, and in fact an almost invariable one,

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* Some practitioners also employ the term "chronic." Sleeping sickness is always chronic, however, and therefore the expression is redundant.

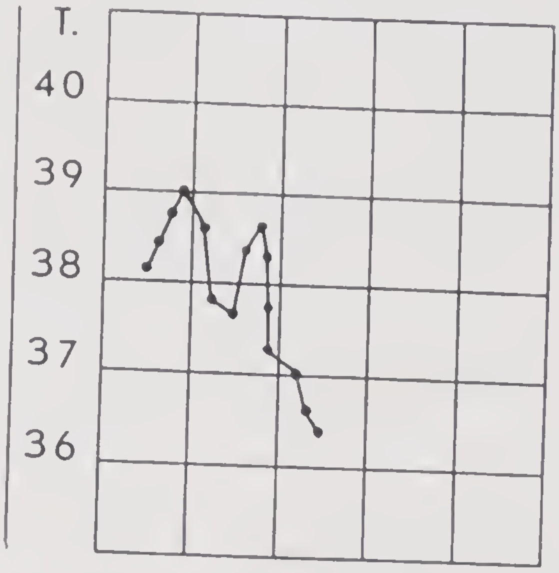


CHART 1. Sleeping sickness in European (Congo, Dr. Broden)

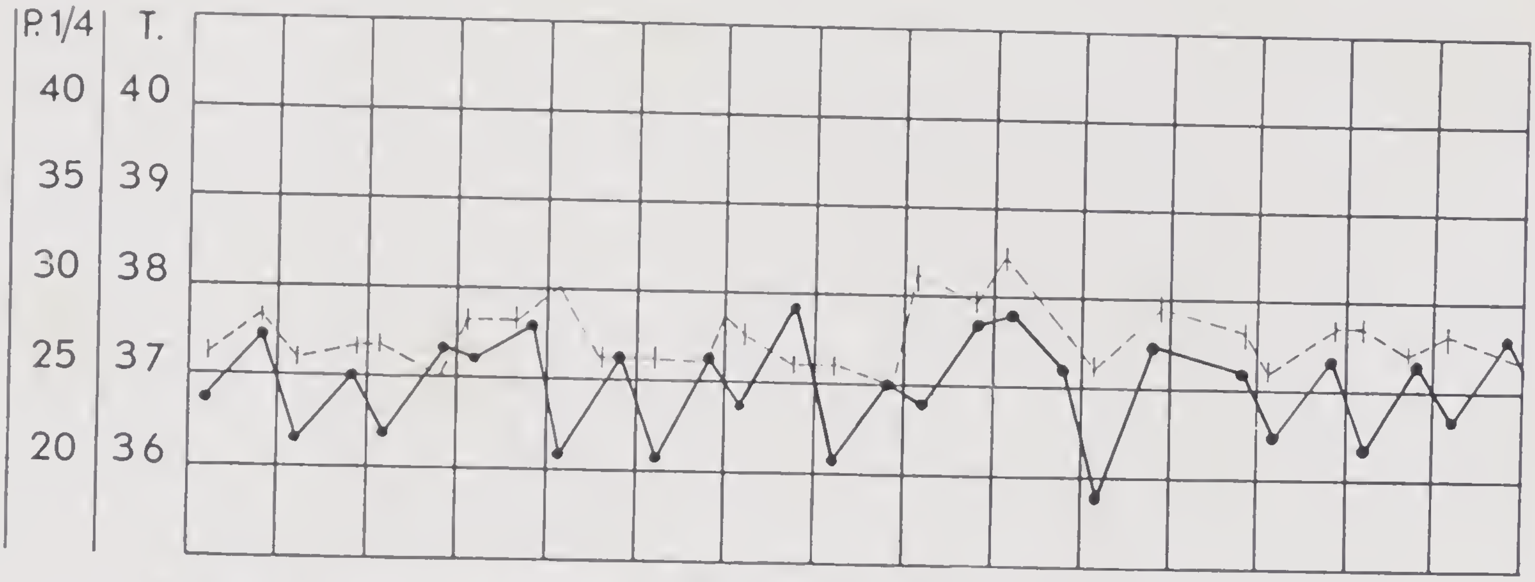


CHART 2. Sleeping sickness. Mild fever. Tachycardia (Dr. Broden)

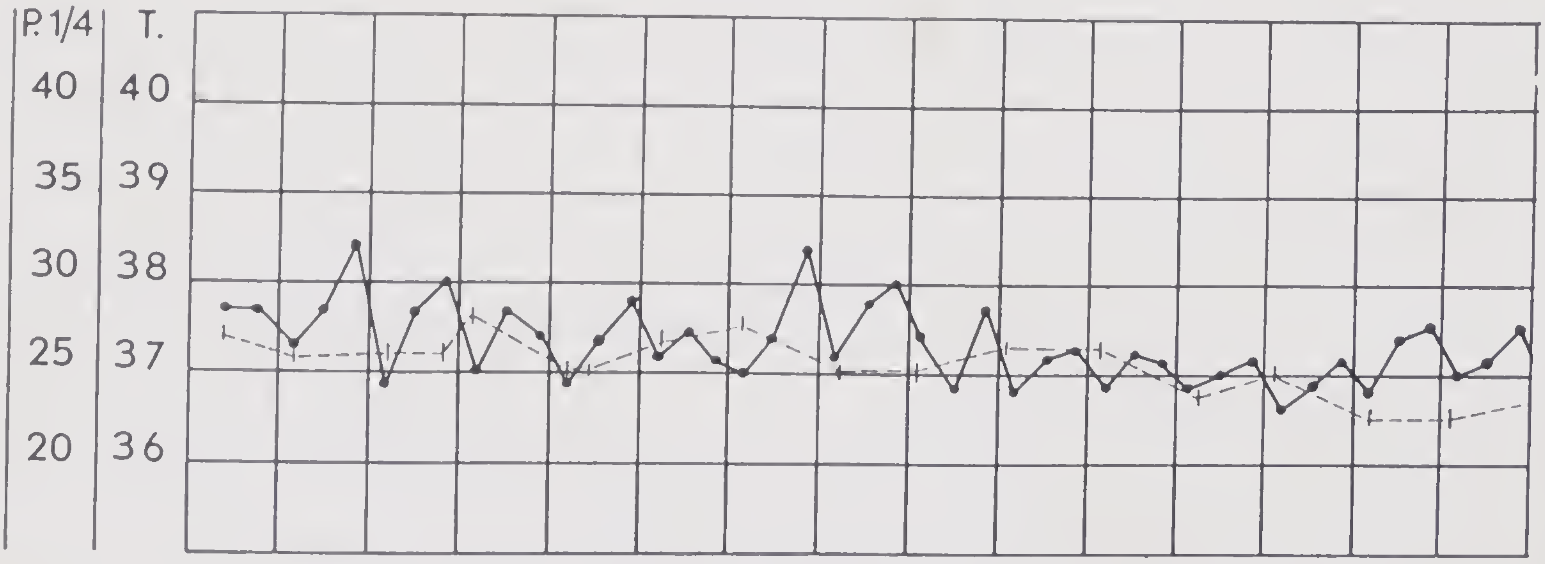


CHART 3. Sleeping sickness. Moderate fever. Tachycardia. (Dr. Broden)

is *adenopathy.* This can be especially observed in the cervical chain. (The inguinal lymph nodes in the Negro are nearly always in a state of chronic inflammation.) These multiple ganglia, of small or medium volume (bean or hazel nut size), are rarely visible. They are painless, without periadenitis or adhesions and there is no suppuration. Their typical consistence is elastic, remittent (like that of a ripe cherry). When pinched they are easily palpable in the depth. Various valuable signs of irregular appearance are quoted from different sources: itching, asthenia, insomnia, neuralgia, anemia, and mild splenomegaly. Sicé insists on the appearance of precocious sexual impotence. Amenorrhea can also be observed, much later on, however. One should note that these various nervous signs, including impotence, are evident chiefly in Europeans, and that Negroes rarely complain about these in the beginning.

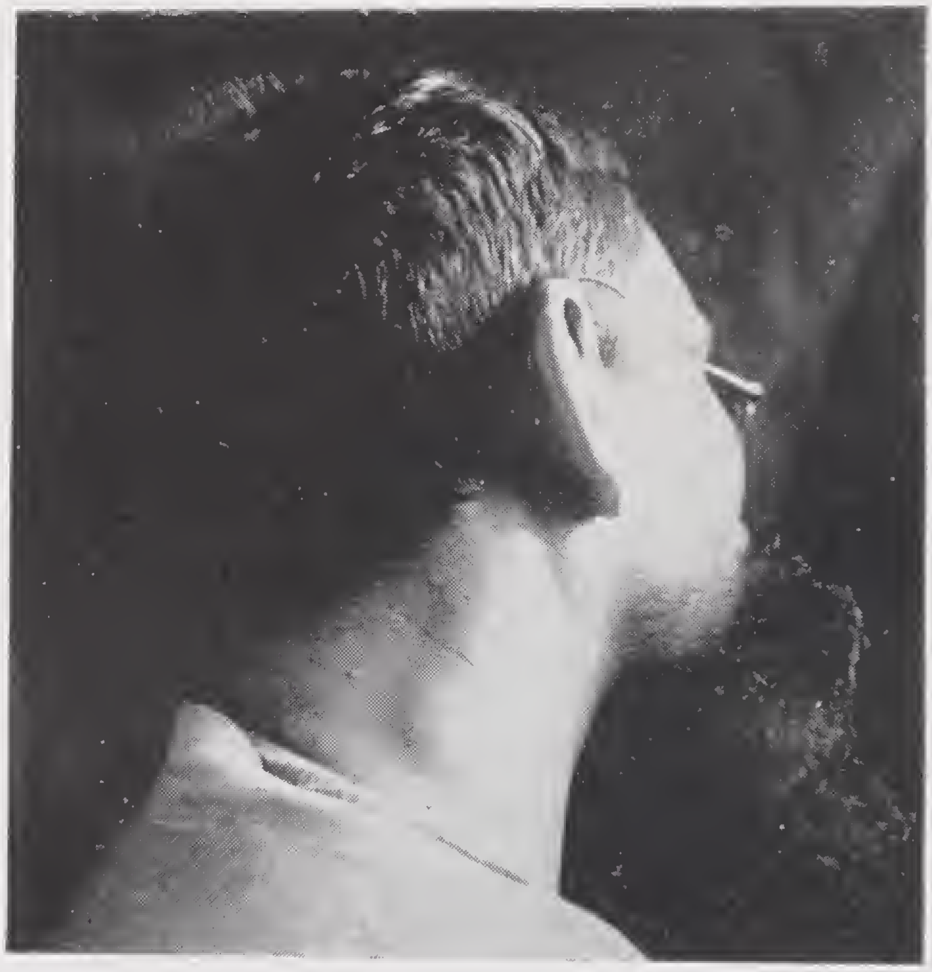


FIG. 7. AFRICAN TRYPANOSOMIASIS: CERVICAL ADENOPATHY
Father R. photographed in 1906 by A. Broden (coll. Tropical Institute, Antwerp)

The key sign, or Kérandel's sign, of deep and delayed hyperesthesia to shocks and pressure, observed by Kérandel on himself, is not constant. Sometimes diarrhea, occasionally with blood, has been mentioned, and also albuminuria. The latter, according to Marqueissac, exists very frequently and disappears with treatment. There have also been cases of edema, usually facial, of uncertain pathogeny and rather infrequent. In rare cases there exist ocular troubles (keratitis, iridocyclitis).

FOOD TECHNOLOGICAL RESEARCH IN
LIBRARY

An interesting and informative exposition of symptomatology may be obtained from the following auto-observation of the beginning of his illness in the Congo by Doctor W.

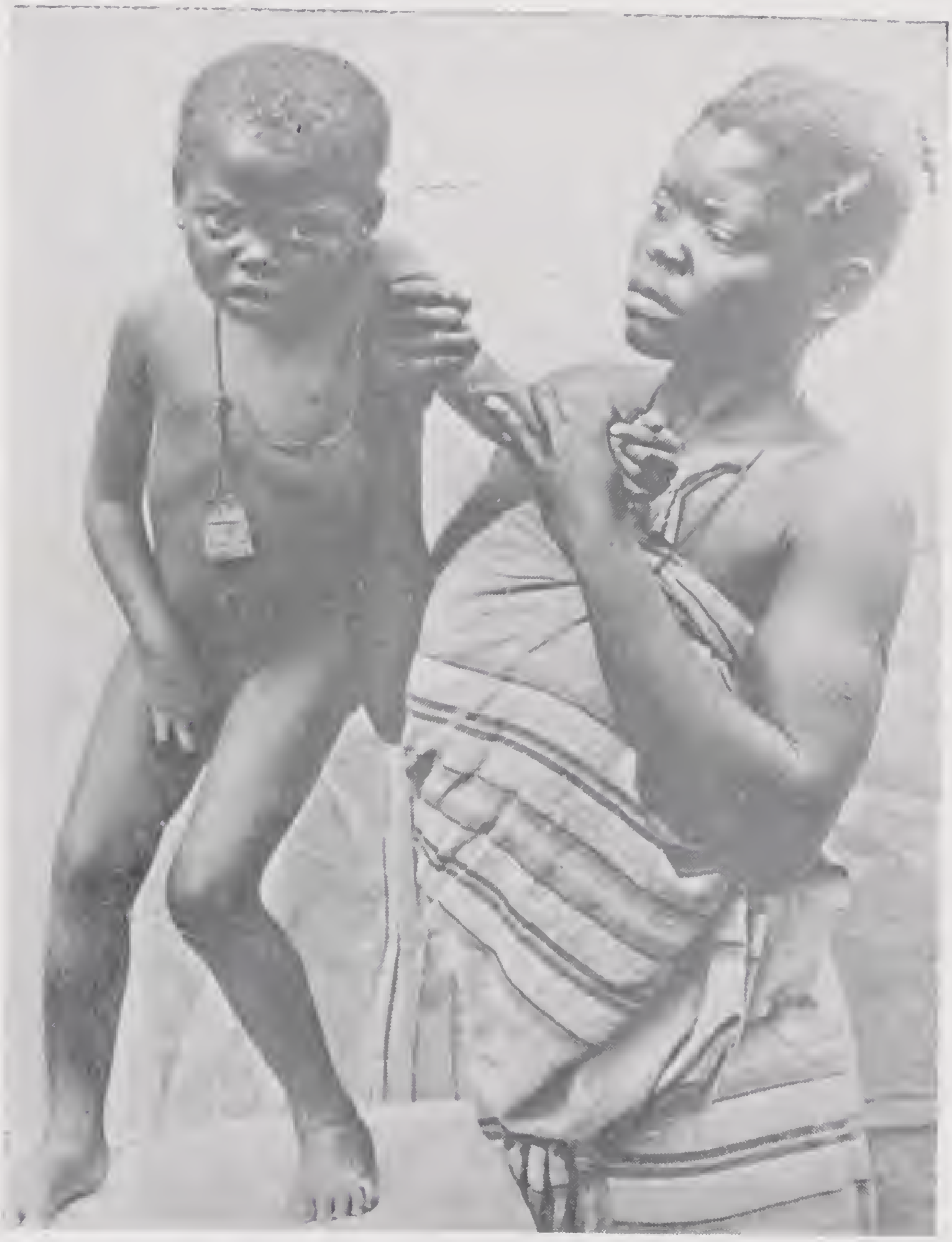


FIG. 8. AFRICAN SLEEPING SICKNESS: NEURO-MUSCULAR DISTURBANCES
Phot. A. Broden, coll. Tropical Institute, Antwerp

July 1935: Irregular fever attacks limited to 38.5 C. in the evening, descending to about 37 C. in the morning, during 4 to 6 days, accompanied the whole time with general discomfort and headache. Slight shivers. Fever is not accompanied with sweating. Periods without fever last from 4 to 8 days. Persistent fatigue and general weakness. In July and August several treatments with quinine and atabrin gave no result. Toward the end of August or beginning of September the pulse often exceeded 100, even without fever. Fever attacks diminished one to two days. Fatigue became more marked. In September attention was drawn to large but painless cervicle ganglions. End of September, on several parts of the thorax an erythematous rash, annular and nonpruriginous, was observed. From September on, tremors of the hands appear. The diagnosis was settled by blood examination and puncture of enlarged lymph glands. Kérandel's sign was not in evidence.

2. *Nerve symptoms.* Certain authors attach little importance to the chronology of this illness. Nevertheless, the period of nerve symptoms appears only after several months and then steadily progresses. Preliminary symptoms may continue, but the lymph glands become less typical because of fibrosis and atrophy. Fever becomes less frequent. In general the patient remains able to walk about and render service.

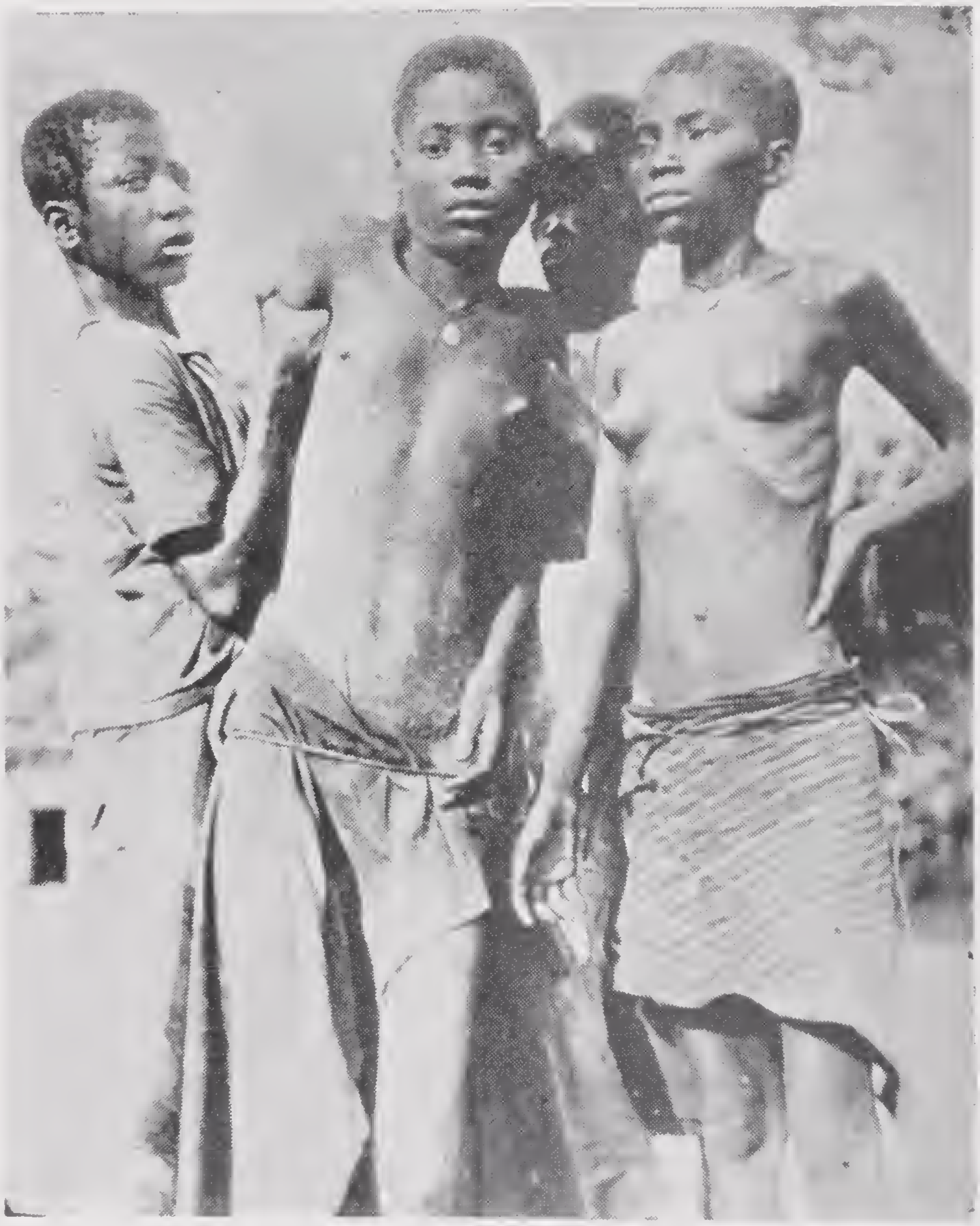


Fig. 9. African Sleeping Sickness
Phot. A. Broden, coll. Tropical Institute, Antwerp

Troubles of the secondary stage concern the different cerebral functions. Psychologic disturbances with marked change of character include apathy, negligence, and irregularities in professional activities. With the progression of these symptoms, different forms of psychic trouble are evident, such as fits of mania and mental confusion, while an expression of vacancy is most characteristic.

With regard to motor nerves, the walk becomes dragging, there are tremors of the hands and tongue, with slurred speech, grimacing, choreic movements and sometimes convulsive attacks of Jacksonian or general type. True paralysis, mono, hemi or paraplegia are infrequent and, besides, may result from complications. Reflexes vary; the Babinski sign is missing. There are no pupillary troubles as a rule, and Romberg's sign is seen much later.

As far as sensibility goes, nothing very precise has been noted. Headache is frequently mentioned, while pruritus may be very severe.

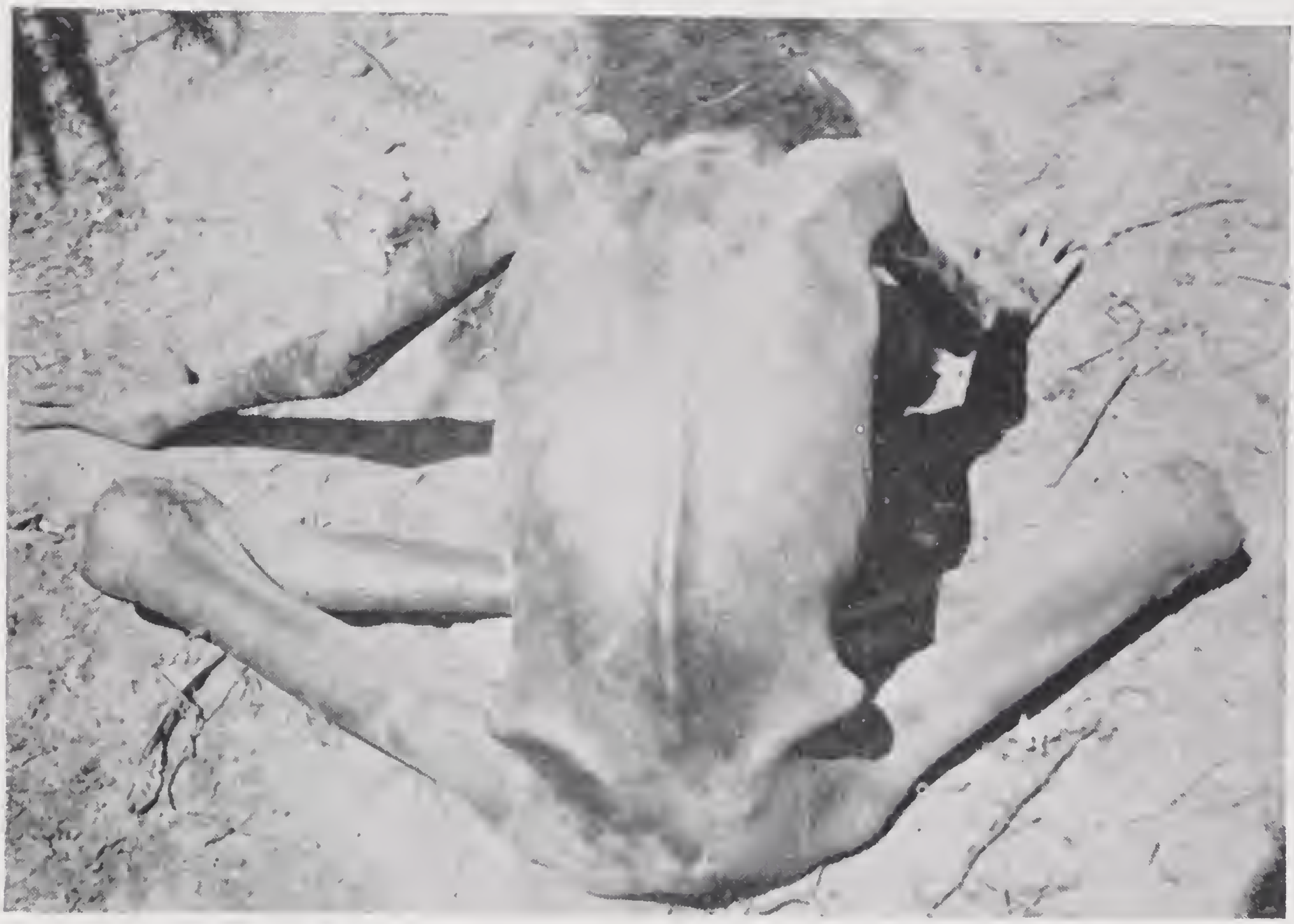


FIG. 10. AFRICAN SLEEPING SICKNESS: TERMINAL CACHEXIA
Coll. Tropical Institute, Antwerp

3. *Tertiary stage.* There finally appears progressively, and also much later, a daily somnolence at first compatible with a normal existence. The patient is easily roused, and also by nature's exigencies. Later this lethargy intensifies and the subject become a "sleeper," although this state may be accompanied by insomnia and nocturnal excitement.

This period can also present ocular trouble, papilledema, atrophy of optic nerve, and sometimes iridochoroiditis. French observers have drawn attention to the frequency of ocular troubles of other origin among certain African populations (syphilis, nicotine poisoning, and avitaminosis).

Nutrition and the major functions remain satisfactory for a considerable time. If he is well cared for, the patient remains sufficiently corpulent, sometimes too much so, having an appearance of dropsical puffiness. Bulimia, which is sometimes observed, is an unfavorable sign. Subsequently, however, cachexia develops and the subject dies in a coma or as a result of complications and accidents.

Temperature varies during the course of this second period, and there can be an absence of fever. Hypothermy or, on the other hand, hyperthermy as well as epileptiform attacks are often noted toward the end. The rate of abortions exceed the average in pregnant females suffering from sleeping sickness.

The foregoing description largely concerns the cerebral and most frequent form of this affection. Sicé indicates more uncommon forms.

1. Radiculoneuritis.
2. Medullar (paraplegia, impotence, absence of sphincter disorders).
3. Cerebellar, extrapyramidal.

Tr. rhodesiense infection is characterized by intensity of general infectious phenomena. Fever, rapid emaciation, weakness, noticeable swellings either of the face or ankles. Myocardia is marked (tachycardia, circulatory weakness). The nervous system changes rapidly, acute mental signs are often observed, convulsions are followed by death. In some cases changes of the cerebrospinal fluid develop without major clinical symptoms. Enlarged lymph glands are less typical than in the more chronic form of *Tr. gambiense,* and can be noted more especially at the epitrochlea and armpits. Parasites are more abundant in the blood.

EVOLUTION AND PROGNOSIS

Tr. gambiense infection is always of long duration, normally several years, but it is difficult to say if it is inevitably fatal. Before modern methods of treatment, patients with impaired cerebrospinal fluid and nervous ailments, clinically appreciable, succumbed in spite of atoxyl. The question is whether the period of nervous affection is inevitable. In Nigeria, there has been noted a mild form which is fatal only by complications, pneumonia, dysentery, etc., being invariably frequent. French authors have noticed that evolution is very slow in Africans brought to France, soldiers in particular.

Prognosis of the *Tr. rhodesiense* infection is especially serious and evolution fairly rapid (one year).

DIAGNOSIS

The clinical diagnosis may be extremely difficult. Irregular fever, intractible to antimalarial medication, must be watched. The eruption may be a precious warning with European patients. Palpation of the lymphatic glands, when they are typical, is a very valuable indication and not to be neglected even if the microscopic examination is not actually positive for the moment. Vacant expression, the walk, and lethargy are important signs. It is possible to mistake these symptoms for epidemic encephalitis, but in the latter there is rigidity, parkinsonism and an acute beginning. Nevertheless, a laboratory diagnosis must be reached with absolute certainty, the need for which arises from two imperative reasons.

1. Grave illness of long duration, weighing heavily on the patient, and calling for treatment which is not devoid of risk.
2. Illness which can easily pass unnoticed, especially with Negroes.

This last point leads to social diagnosis, which depends on systematic examination of the entire population with microscopic control.

Social Diagnosis. This is based on the palpation of lymph glands followed by their puncture, and on examination of nonganglionous subjects suspected for other reasons (psychic disorders). There is a growing tendency today systematically to examine the blood of the entire population, at least in the most resistant foci (thick drop preparation).

Social diagnosis is legally based in the Belgian Congo on health regulations and especially on the obligation to carry a medical passport, regularly controlled, and also on the doctor's right to convoke the population for examination. The gravity of the endemic justifies a certain coercion and the establishing of a nominative and familial medical census.

These examinations, which are repeated every three to six months, according to possibilities, are now well accepted by the natives. Analogous schemes are in force in other countries.

Precise or laboratory diagnosis. Hematology: Anemia and mononucleosis are not characteristic. Autoagglutination, almost regular in Trypanosomiasis, is often seen in "healthy" blacks. Formolgelification also lacks specificity. (Leprosy, leishmaniasis, schistosomiasis.)

Parasitology: Parasite research is the method of choice.

1. *In the blood.*

(a) Drops or ordinary smears are insufficient for *Tr. gambiense;* they are of more use in *Tr. rhodesiense.*

(b) Thick drop preparation is 50 per cent successful.

(c) Triple centrifugation (Martin, Roubaud and Le Boeuf).

This is practiced on 10 cc. of citrated blood. A first centrifugation, carefully watched (less than 1,000 revolutions), precipitates the red globules. Floating plasma is then centrifuged at a speed of 1,500 revolutions (10 minutes) which assures the precipitation of white globules, microfilariae and sometimes already a few trypanosomes. The plasma, thus treated, is again finally centrifuged at 2,000–3,000 revolutions (15 minutes) and the residuum is examined. It will contain trypanosomes, thrombocytes, and possibly spirochetes. Broden states that he has obtained by this method almost 80 per cent success. Its relative complication renders it impractical for social diagnosis. It is reserved for special cases, such as Europeans under observation, certain nervous cases, and, above all, for therapeutic control.

(d) *Inoculation.* Into guinea pigs and monkeys. Very impractical method, cumbersome, and uncertain, given the variable pathogenicity of *Tr. gambiense.* Animal inoculation is necessary nevertheless, in order to differentiate between *Tr. rhodesiense* and *Tr. gambiense,* and to appreciate the arseno or chemico resistance of a strain.

(e) *Hemoculture.* Method which should be employed more frequently. This is already in practice at Leopoldville, rendering important services, but is possible only in suitably equipped centers (Brutsaert and Henrard's technic).

2. *In bone marrow.* Sternal puncture does not appear of much use, but can, however, constitute a supplementary resource.

3. *In the lymph glands.* This method gave Broden 88 per cent of success (including cases without palpable glands). The technic is simple. As material: fairly short needles of medium thickness (0.7 mm.), dry sterilized or, in any case, having a free canal. Dry syringe which is not used for the puncture. Technic: immobilize a ganglion, puncture boldly in two or three directions (without withdrawing) while pressing the ganglion between thumb and finger. The lymph thus obtained, which should contain only the minimum of blood, is freshly examined for ten minutes if necessary (use a chariot). Staining is unnecessary.

4. *In the cerebrospinal fluid,* research has not been very satisfactory, giving a positive result only in advanced cases (70–80 per cent of the latter).

Serology is still little employed. Deviation of the complement is of use in veterinary medicine, especially in cases of dourine. It has also been used in human medicine. It may serve for the diagnosis, but not for therapeutic control, as the reaction remains positive after cure. Certain authors use the test of adhesion of globules or blood platelets to trypanosomes in the presence of a specific serum. In the Belgian Congo, positive reactions to Bordet-Wassermann, Kahn, etc., in sleeping sickness patients are considered as related to concomitant syphilis or yaws. In the secondary stage, a reaction is observed of cerebrospinal liquid to Benjoin or to colloidal gold in the paralytic zone, but the Bordet-Wassermann reaction remains negative (Rodhain).

Diagnosis of the period. The psychiatric or neurologic study of the patient is useful, but there is no doubt that examination of the cerebrospinal fluid gives quicker and more precise results. Since 1908, this fact has been established by the work of Broden and Rodhain who demonstrated the prognostic significance of the method. Although actually prognosis of the secondary stage has improved since the introduction of tryparsamide, it is none the less true that in this case, treatment is longer and more difficult. It is necessary then, to specify before treating by lumbar puncture, or in rarer cases, occipital puncture, the degree of modification in the nervous system. This can also serve as an indispensable control after treatment. It seems wise to sterilize the blood before practicing lumbar puncture. Let us note that the meningeal reaction has only a relative specificity, as have the majority of pathologic signs. One must interpret them with prudence because they may be related to syphilis or recurrent fever.

Pressure is usually increased in the secondary stage. Cerebrospinal liquid, however, remains clear. Advanced cases sometimes show only a certain opalescence when held to the light. A purulent aspect indicates complications (meningococci, pneumococci, etc.).

Cytology. Normal cerebrospinal fluid contains, at the most, two cells (lymphocytes) per cubic millimeter. In the first stages of illness, the number of cells remains at this constant. Till the second stage it never exceeds 4 or 5 cells, but in advanced cases one sees an increase. At first, small lymphocytes appear in dozens per cu. mm.; they are then joined by large lymphocytes, monocytes, and large endothelial cells.

The appearance of Mott cells is very characteristic and relatively pathognomic. They are vacuolar and vary in size (muriform or morular cells). Usually they are found only when there are considerable numbers of cells.

Technic. One employs the classic methods of direct examination in a calibrated chamber. One must not forget to examine the cerebrospinal fluid immediately in order to avoid autolysis of cellular elements.

Nagcotte Cell (depth 500 microns), of which each rectangle counts one twenty-fifth cu. mm.; therefore, divide by 10 after counting 8 rectangles. The method is suitable for slightly altered fluids.

Fuchs-Rosenthal Cell. The total quadrate of this comprises 3.2 cu. mm.

We recommend the addition of a trace of polychrome blue or toluidine blue to the cell for easier observation of the nuclei. If blood is present, dilute with the Turck liquid used for counting white globules.

Generally speaking, one may say that cellular reaction increases quantitatively and modifies itself qualitatively with the progress of the disease.

The presence of morular cells or trypanosomes is a grave sign. Formerly, any patient who had over 5 to 10 cells per cu. mm. was considered a serious case. According to Sicé, the cellular reaction which is more precocious and variable than that of hyperalbuminosis, is less significant for the prognosis than the latter. The first would be a sign of meningovascularitis and the second would be that of meningoencephalitis. This view seems corroborated by the practice.

Hyperalbuminosis. It is admitted that the cerebrospinal fluid contains a maximum of 22 mg. of proteins per 100 cc. The limit of the primary stage had been fixed by Broden and Rodhain at 25 mg. Hyperalbuminosis in trypanosomiasis usually remains moderate, and more or less parallel to the lymphocytosis. In only mildly advanced cases, one finds from 30 to 40 mg., later on, 60 to 80, but rarely more than 100 mg. per 100 cc.

Dosage. The small rachialbuminometer of Sicard and Cantaloube is used in various countries. Four cubic centimeters of fluid are placed in the tube and heated to 90 C. in a bain-marie. Add 12 drops of trichloracetic acid at 33 per cent. Allow to cool for five minutes, then closing the tube tightly, mix the precipitate thoroughly by shaking the tube. Let the contents stand for five hours and note the height of the sediment in the graduated tube.

The method of Mestrezat is more rapid. One or 2 cc. of fluid is added to 0.1 cc. of HNO_3 and the mixture is compared with a standard measure obtained by means of human serum of a known proteic composition.

Rapid tests (globulins):

1. Pandy's test. Reagent: Crystallized phenol saturated in water. Decant the upper part. Technic: 1 cc. of reagent in a narrow tube. Let one drop of fluid fall. Normally, there is no opalescence. This is estimated empyrically at +, ++, +++.
2. Weichbrodt's test. Add 0.3 cc. of $HgCl_2$ pure solution at one per thousand to 0.7 cc. of fluid. Wait a few minutes. Cloudiness is abnormal. We give also Boveri's test which is really an abbreviated dosage of proteins. Normally it takes 5 to 6 minutes for 1 cc. of liquid to discolor 1 cc. of $KMnO_4$ at 1 per 10,000. One notes: 2 minutes, ++; 3–4 minutes, +; 5–6 minutes, ?; exceeding 5–6 minutes, normal.

Differential Diagnosis. During the fever stage it may be mistaken for various other affections: malaria, recurrent fever, leishmaniasis, Hodgkin's disease, etc. In addition to specific signs of these various affections, trypanosome research would be decisive. In the secondary stage, different nervous states can lead one astray as much by the clinical aspect as by cerebrospinal lymphocytosis: syphilitic meningoencephalitis and various virus encephalites. Concerning general paralysis, apart from the classic clinical signs, one must be guided by blood tests and the cerebrospinal fluid (Bordet-Wassermann and Kahn). The Benjoin test and gold test are positive in sleeping sickness in the paralytic zone. The Bordet-Wassermann reaction appears specific in syphilis.

The Mott cells in cerebrospinal fluid are pathognomonic of sleeping sickness. Benign lymphocytic meningitis offers a cytologic picture which could be deceiving, but the clear-cut and resolutive clinical allure is characteristic. Any manifestation of psychosis should be considered with a certain suspicion, and the clinical and parasitologic indications should be controlled. Experience has shown that on several occasions colonials returning from the tropics have been diagnosed and interned as general paralytics, whereas it was really a question of trypanosomiasis.

TREATMENT

Treatment of trypanosomiasis is essentially chemico-therapeutic, which does not mean that the general hygiene of patients and the treatment of possibly associated diseases, such as malaria, intestinal worms, and syphilis, is to be neglected.

General Rules. If possible, treatment should begin in the first stages or, in any case, before serious modification of the cerebrospinal fluid takes place. Treatment is then surer, quicker, and less dangerous. Cases must be energetically treated from the beginning. In advanced cases, with modified cerebrospinal fluid, a more prudent and prolonged therapeutic is needed. As a rule, associated medication, either contemporary or successive, is most successful. A true synergy in the pharmacologic sense of the word has, however, not been proved in man.

Control of Results. This is obtained clinically, in the first place, but chiefly, given the conditions of practice in Africa, by verification of persistent blood sterilization and a normal cerebrospinal fluid. For this purpose, then, one uses the known methods of diagnosis. Negative examination and normal cerebrospinal fluid (verified each three months, then each six months) indicate an apparent cure; after an eighteen-month period of observation, a definite cure can be declared.

Active medication belongs to three series:

I. *Arsenical series:* There are a number of products of a given activity among inorganic arsenical compounds and also among organic aromatic cyclical compounds. Rectilinear organic compounds (such as sodium cacodylate) are inefficacious. It is to be observed, then, that in the arsenical series, the element is not everything; it is the molecular structure which is important. Among the thousand of synthetic organic arsenical products that exist, only a few are actually employed.

II. *Antimonial series:* A great number of antimonial compounds show trypanocide properties, but here again the molecular structure plays an important role. Trivalent antimony alone has provided quite active combinations against trypanosomes and the pentavalent antimony is, on the contrary, employed against leishmaniasis.

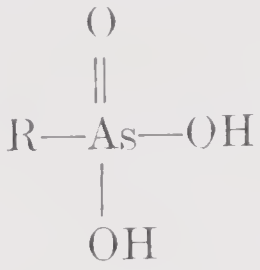
III. *Series of organic substances:* Compounds of carbon, hydrogen, oxygen azote without chemico-therapeutic elements. It will be understood that in this case the molecular arrangement is essential, very often minimal structural variations diminishing activity in a marked manner.

I. *Arsenical Agents*

1. *Inorganic compounds:* Arsenious acid and its salts (trivalent arsenic), arsenic trisulfide (orpiment), have a certain activity, but too reduced or associated with too great a toxicity, to advise their use. The inorganic pentavalent derivates (arsenic acid) are not important in practice.

2. *Organic arsenicals:* Only the cyclic derivatives are used. Sometimes

they are pentavalent of the general formula



$$R{-}\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OH}{|}}{As}}{-}OH$$

in which R is usually a phenyl radical more or less substituted. Theoretically, one can derive these products of arsenic acid (pentavalent).

$O{=}As{\equiv}(OH)_3$ by replacement of a hydroxyl by a phenyl radical or even aromatic arsines at the maximum point of oxidation.

$C_6H_5{-}AsH_2$ phenylarsine (derivative of AsH_3 by substitution of an H by C_6H_5).

$C_6H_5{-}As{=}O$ oxyd of phenylarsine (trivalent As)

$C_6H_5{-}AsO{-}OH_2$ phenylarsine acid (pentavalent As)

Trivalent substances of the same type are also used, arsine as above or chlorarsine $R{-}As{=}Cl_2$ where Cl_2 replaces O. Finally, the complete reduction of arsenic acids result in arsenoic compounds

$R{-}As{=}As{-}R$ (606–914, etc.)

well known in syphilography and also active in trypanosomiases.

Arsenic Pentavalents.

(a) *Atoxyl* (sodium arsanilate or sodium p. aminophenylarsinate)

$NH_2{-}C_6H_4{-}AsO_3NaH, 3H_2O$ (1–4)

Description. White crystalline powder soluble in six parts water, of 293 molecular weight, containing 25 per cent arsenic.

Method. Solution of 10 per cent fresh and not boiled, in subcutaneous injection, in the muscles or in the veins.

Posology. In the first stage, 20 mg. per kilo of body weight, i.e., about one gram for an adult. Repeat dose once a week for ten weeks. Secondary stage: 10 mg. per kilo, i.e., 500 mg. for an adult. Repeat weekly or every five days (20 times). Successive treatments after intervals of three weeks' rest.

Therapeutic action. This is favorable in the first stages. Trypanosomes disappear in a few hours, the fever, general discomfort, glandular troubles are no longer apparent, and according to Sicé, a cure is obtained in 62 per cent of cases, which confirms our own experience. At the secondary stage, however, results are less favorable, and one sees, in most cases, improvements which are not maintained. Very advanced cases, called tertiary stage cases, do not benefit, or only very slightly, from the treatment (which can even be harmful).

Toxic phenomena. Strong doses sometimes cause gastralgic accidents and fainting fits, which do not last and are, moreover, not particularly dangerous. In general, the dose has only to be diminished (750 mg. instead of one gram) and morphine used against the attack.

With certain patients, especially in the secondary stage, repeated treatment will cause a grave and irreversible optic neuritis, often leading to blindness. Thus, as with other arsenical pentavalents, it is imperative to verify the patient's clearness of vision, and ascertain if there are suspicious signs existing such as hazy or failing sight, ocular pains, etc.[*]

(b) *Arsacetine* does not differ from atoxyl except by acetylation of the link NH_2 which becomes $NH—CO—CH_3$. It has similar qualities but is rarely used.

(c) *Glyphenarsine* Ph. B. IV, tryparsamide, tryponarsyl or sodic N-phenylglycinamide-p-arsinate. This substance differs from atoxyl simply by the elongation of the aminated chain which contains the amide of glycocolle or glycin giving the following formula: $CO—NH_2—CH_2—NH—C_6H_4—As—O_3NaH, {}^1/_2H_2O$ (1–4).

Description. White crystalline powder soluble in 2.5 parts of water containing about 25 per cent arsenic.

Posology. Fresh solutions (unboiled) from 30 to 40 per cent for intravenous injections, and from 15 to 20 per cent for intramuscular injections should be used. The latter are inadvisable.

Note that these solutions of 30 to 40 per cent demand care concerning the final volume. The solution must be made in a measured recipient or one must apply Chesterman's formula: n. Gm. tryparsamide plus 2n. Gm. water gives a 40 per cent solution.

Tryparsamide toxicity is very different from that of atoxyl in spite of the mild chemical modification. The following is a schema taken from Launoy and Egler.

Compared toxicity:	Atoxyl—	Tryparsamide—	Orsanine
Rabbits. Dose in mg. per kilo			
Lethal 100 per cent	200	850	400
Tolerated 50–60 per cent	50	750	250
Weekly repetition	30	400	200
Mice. Dose in mg. per 20 Gm.			
Lethal 100 per cent	15	85	45
Tolerated 50–60 per cent	7	40	25

Although these figures are probably too low, the comparison made by the authors is valuable and shows a remarkable difference of toxicity. The doses mentioned for humans seem high also. The Belgian pharmacopeia lists 1 to 3 Gm.,[†] while in colonial practice one often uses 60 to 70 mg. per kilo, i.e., about 3 to 4 Gm. for adults in good condition. Human subjects have even been given doses varying between 100 and 230 mg. per kilo. Here again, at the secondary stage, one readily uses more moderate doses (35 mg. per kilo which means practically 2 Gm.)

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[*] It should be noted that the disease itself can cause ocular trouble. The patient should have ocular examination before any treatment. In case of ocular trouble, arsenic is not prescribed but calls for constant surveillance.

[†] In actual practice the dose is never fractioned.

As regular treatment during the primary period, ten weekly injections diminishing from 4 or even 4.5 Gm. to 3 Gm. and more rarely to 2 Gm.

At the secondary period the maximum dose is limited to 2 Gm. except for the first one or two injections which reach 3 to 4 Gm. The dose of 2 Gm. in this case is continued for 20 to 40 and even 100 weeks, according to the clinical and humoral state. Chesterman advises strong doses even at the second period, but this has frequently caused ocular complications.

Therapeutic results. At the primary period, definite cures frequently seem to result, although this is contested by French authors who in actual practice use a dose inferior to that which we recommend. Certain series give 100 per cent cures.

At the second period (and this is where one observes the great advantage of this product over atoxyl) one can expect 50 per cent of cures, and even bedridden cases have benefited by the treatment.

Toxic complications. Repeated doses bring the risk of optic neuritis and the same precautions must be taken as with atoxyl. Exfoliative dermatitis is rare. Sudden deaths have been recorded.

(d) *Acid hydroxy-aminophenylarsinic compounds.* To this series belongs the *Stovarsol* (Goyl), practically inactive, and its isomeric *Sodium orsanine:* $CO—CH_3—NH—C_6H_3—OH—AsO_3NaH,\ 5H_2O$ (1–2–4). In this product, p-acetyl-amino-o-hydroxyphenyl-arsinate of sodium, the passage in position para of the acetylamino link causes the trypanocide properties to appear.

Orsanine, greatly in use in French colonies, is a good sterilizer and at the secondary stage resembles tryparsamide. It is, however, less active in cases of pronounced alteration of the nervous system. It is more toxic than tryparsamide but may be employed in smaller doses, that is, between 1 and 2 Gm. repeated, according to a schema approaching that of atoxyl. Deaths have also been recorded after its use.

Cyclic Arsenical Trivalents.

(a) *Arsenoic compounds.* These are not employed to any great extent despite their extensive experimental activity in small animals. Their action, which is brilliant at the primary period and which has been able to ensure the maximum sterilizing therapy (in Ehrlich's meaning, i.e., cures effected by a small number of injections) is infinitely less effective at the secondary period.* Their use would be obligatory only in cases accompanied by concomitant yaws or syphilis.

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* Doubtless due to less diffusibility toward the nervous centers than tryponarsyl or orsanine which renders the cerebrospinal fluid trypanocidal in vitro.

(b) *Arsine oxide: Mapharsene, neohalarsine, etc.* These products which enjoy the favor of syphilographers do not appear very beneficial here (Van Hoof, oral com.). We will quote, however, p-arsenosophenylbutyric acid or $O{=}As{-}C_6H_4{-}(CH_2)_3{-}COOH$, studied by Eagle with the help of specialists in several African countries. This therapeutic agent gives approximately 90 per cent cures at the first period with a total dose of 6 to 7 mg. per kilo (ordinarily 0.4 mg. per kilo. per injection with a maximum of 2 mg.). The tolerance seems good. The best administration is intravenously, or, if necessary, intramuscularly. Rapid treatments of twelve to fourteen times, 0.5 mg. per kilo, or six to seven times, 1 mg. daily, seem ideal, but administration at wider intervals seems equally effective. The treatment is active in cases of arsenoresistance (Van Hoof).

Another trivalent product, Melarsen oxide, according to the same experimenter, is active in nervous cases and in arsenoresistance (oral com.).

II. *Antimonial Products*

1. *Potassium emetic* is the oldest of these products.

Description. Antimoniotartrate of potassium is a white powder, soluble in 17 parts of water, containing 36 per cent of trivalent antimony in a molecule weighing 333.

Posology. One uses a fresh solution, unboiled, of 1 per cent in salt water or glucose which, given intense tissular irritation, can be injected only in the vein. The dose amounts to 2 mg. by Kg., in practice 100 mg., which is reached progressively from 60 to 70 mg. This dose is repeated 10 to 12 times on consecutive or alternative days.

Therapeutic action. Tartar emetic produces a rapid sterilization (16 minutes) but of short duration. Even after repeated doses, cure is unsure and is certainly not reached at the secondary period.

Indications of tartar emetic are those of a supplementary medicine, combined therapeutic, intolerance to arsenic, or arseno-resistance of trypanosomes. Nevertheless, some patients owe their cure to it, Dr. Kerandel for example.

Toxic phenomena. One can immediately note the convulsive cough, and less frequently, vomiting. These incidents call for prudence; rare cases of collapse can take place with even fatal results. At the end of treatment, tiredness, articular pains in the shoulders are often observed.

2. *Other antimonials.*

Difficulty in administration of emetic has given rise to the study of antimonies, easier to employ or less toxic, e.g., *Stibilase* (*Meurice*) and *Trystibine* (*Meurice*), which are antimonial compounds with quinolin bases. The action of trystibine has been judged favorable by Van Hoof. Posology is that indicated for the treatment of schistosomiasis.

The *Fouadine Bayer* derivate of pyrocatechine, which has the advantage over the preceding products of being tolerated by muscular injection, is insufficiently known in human trypanosomiasis, but has a certain activity. It is only an occasional resource.

Anthiomaline Specia (thiomalate of lithium and trivalent antimony) may also be injected in the muscles. Its action is also that of an auxiliary.

As for pentavalent antimonies, derivates of phenylstibinic acid, comparable therefore to atoxyl, etc., these have no practical value in sleeping sickness (see therapeutic of Leishmaniasis).

III. Organic Compounds

Trypaflavine, derived from acridine, and Tryparosan, derived from triphenylmethane, have only an historical interest. On the other hand, a particularly important organic molecule is specialized by Bayer under the name of Germanine, also as Bayer 205, and by the Specia Company under the name Moranyl. (Belganyl in Belgium, Antrypol in England, Naphuride Sodium or Suramin in the U. S.). It concerns a voluminous molecule, grouping each side of a nucleus of urea, various aromatic substituted and sulfoned radicals. Yellow-gray powder easily soluble and employed in a 10 per cent solution in intravenous injections if possible, or, if unavoidable, intramuscular. The adult dose is 1 or occasionally 1.5 Gm. The cure comprises a small number of injections totaling 4–6 Gm. in a few days (5–15 days according to tolerance). The proposed treatment is 1 Gm. each on the first, third, tenth, thirteenth days.

In Nigeria a first trial dose of 300 mg. precedes the active injection. Formerly one began with 500 mg., followed by a normal dose on the next day. Some authorities advise 1 Gm. six times with a few days interval.

Mühlens and colleagues prescribe 1 Gm. each on the first, second, third, seventh and eighth days. If necessary this treatment may be resumed after a month.

Rodhain formulates:

1st day	500 mg.
2nd day	1 Gm.
5th–6th day	1 Gm., or

2.50 Gm. the first week
then each week 1 Gm. up to 5–7 Gm.

Van Hoof (verbal com.) is not in favor of the trial doses. Cases of widespread and chronic cutaneous onchocerciasis sometimes support the treatment badly. It is, however, active against this filariasis (see further).

Therapeutic results. Experimentally, with *Tr. brucei* or small laboratory animals, Bayer 205 has an extremely favorable therapeutic index (200–300)* With regard to man, this index is less fortunate. However, the action against *Tr. rhodesiense* is brilliant, especially in the beginning of infection, while in this case arsenic is less active than with *Tr. gambiense.* With this latter, which interests us particularly, one must decide according to the progress of the disease. At the primary period definite sterilization can frequently be counted on. Van den Branden, however, cites 28 per cent of relapses with a dosage of only 3.5 Gm.

The actual tendency is, in any case, to follow the Bayer 205 with an arsenical or antimonial treatment. At the second period the B 205 acts insufficiently on nervous phenomena, and its prolonged repetition is not without danger (nephritis). It can, however, be employed in association with antimonials and arsenicals and proves then of great utility.

It should also be noted that experiments have shown that B 205 exercises a prolonged protective action in animals because of its slow elimination. Systematic trials made on man by various doctors of the Congo seem to confirm this point but repetition of the treatment ought to be made approximately every three months; hence the method does not appear to be very practical nor, perhaps, inoffensive.

Toxic phenomena caused by B 205 are not very numerous. These have been noted as erythemas, conjunctivites, paresthesias and pains in the extremities followed by desquamation. Fairly often one observes albuminuria, usually mild and of short duration. Nevertheless, it is a fact that authentic nephritis has been noted and that it is necessary to keep a strict watch on the urine. In cases of albuminuria, the injections must be given at longer intervals.

Synthaline and diamidines. After von Jancso, Schern and colleagues had verified that Synthaline (decamethylene diguanidine) had an effect on experimental trypanosomiasis, W. Yorke and colleagues studied other derivates of guanidine and a whole series of rectilinear or cyclic guanidines. Guanidine is a strong base, the diamidines have basic extremities and a central carbon chain relatively inert and of varied type.

The guanidines and rectilinear diamidines exert a marked action on the glucidic metabolism, but also a definite hepatic and renal toxicity, the first of which being the decisive factor in its rejection as antidiabetic.

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* By therapeutic index is meant the quotient of the tolerated dosis T by the curative dosis C. The product becomes better with the increase of the quotient: compare

$$T/C{:}10/10 = 1, \text{ with } T/C{:}20/2 = 10$$

It seems logical in experimental medicine to consider as T the dosis which gives 50 to 60 per cent deaths among experimental animals. C is the dosis which cures 80 per cent of moderately infected animals.

Although the pharmacology of cyclic derivates is fairly similar, they are, however, more easily manipulated. They exercise a depressing action on the blood pressure and provoke in man, either by this mechanism or by other means, a whole series of troubles which disappear rapidly while at the same time the tension rises again. We advise a slow injection if venous. If the product is not too irritant, the muscular injection is still better.

Adrenaline acts as prophylactic or curative of these troubles. Trypanocide activity of these products is brilliant with experimental animals in vivo: chemotherapeutic index 30 (for Stilbamidine); in vitro lethal limit: 1/256 millions (synthaline). In practice one uses in human medicine:

Stilbamidine (see Kala-Azar).

Pentamidine. 4-4′-Diamidino-diphenoxypentane. It is used in doses of 1–2 mg./Kg. (which amounts to 50–100 mg. for adults) in 8 to 12 daily doses. Slow injection (see above).

The effect is good in the primary stage of illness, but as soon as the cerebrospinal fluid is clearly modified (10–30 cells by mmc.) its action is weakened and much inferior to that of Tryparsamide. Prophylactic action is considered further.

Propamidine. 4-4′-Diamidino-diphenoxypropane. Similar action but greater toxicity. Also used as local antiseptic in general medicine.

Routine treatment of the disease: During the first period: 4 to 6 injections of Bayer 205 at 4 to 5-day intervals, followed if necessary by 10 weekly injections of tryparsamide (4–3–3 then 2 Gm.). During the second period: series of 20 weekly injections of tryparsamide (2 Gm.) repeated after three weeks of rest according to the state of the fluid. It is useful to precede this treatment by 2 or 3 injections of Bayer 205.

Intraspinal treatments have shown no special benefit, and more than one has proved dangerous.

Intracarotid treatment. This particular method of introduction of tryparsamide has not been used in general.

Chemotherapeutic mechanisms in trypanosomiases.

The question is too complex for extensive development here. The reader will find details (bibliographic, historic, and experimental) in the works published since 1929 by W. Yorke and colleagues. It may be noted, however, that with the usual products, parasites seem to be destroyed by direct fixation on their protoplasm either by the product itself (immediate direct action) or by a derivate of metabolic origin of the latter (mediate direct action). It is evident that the various chemically active types might injure the different fermentary functions or systems although this is difficult to ascertain with precision. On the contrary, an indirect action by stimulation of cellular defensive mechanisms (or humoral) is not established, and is, besides, irreconcilable with the rapidity of certain cures. As for the processes of the immunity which follows chemotherapeutic intervention, they are secondary to the liberation of antigen resulting from direct destruction of germs. This immunity is, besides, only temporary, and does not play an indispensable part in the cure. It can, however, help.

as is particularly the case during infections with relapses calling for repeated treatment. However, it is without causal importance in what Ehrlich called the "therapia sterilisans magna," i.e., the acute cure of acute infection.

Concerning the reality of direct action, the following may be noted: (1) If we inject a noninfected rabbit with an arsenical, either tri- or pentavalent, its serum becomes trypanocide in vitro. With a trivalent arsenical, this property immediately reaches its maximum titer; with a pentavalent derivate, the titer rises rather slowly, and in either case it diminishes rapidly.

In a healthy animal there must not be the least mechanism of defense but only pharmacologic processes, distribution and eventually transformation of the product. An interesting corollary is that in vivo arsenical trivalents rapidly sterilize the blood, pentavalent derivatives being of slower action. These facts tend to argue a transformation in vivo of pentavalents (see further).

(2) In putting into contact in vitro (37 C. serum medium 24 hours) normal trypanosomes, and active products in vivo, one notes that certain compounds (arsenical trivalents, acriflavine, emetic tartar) have a considerable trypanocidal activity. This can be seen at concentrations of $1/n$ millions (n may be 50–100–400). Such concentrations of arsenic are to be found in the blood for twenty-four hours and longer after treatment. The disappearance of parasites is thus easy to explain. The destruction in vitro of trypanosomes excludes with certainty any intervention of the carrier. On the contrary, arsenical pentavalents are active only at concentrations which are difficult to maintain in vivo (1/1600). Their action in vivo, then, seems to be in relation with a partial transformation into trivalent As. The reduction of a compound of the type $R{-}As.O{-}OH{-}OH$ into $R{-}As{=}O$ or $R{-}As\ (S{-}R')_2$ gives very active products in vitro. Such reductions may occur in the organism through substances of link SH. These transformations explain the comparative slowness of sterilization by arsenical pentavalent products or else of the appearance of maximum trypanocidal strength in the blood of a healthy animal. It has been known for some time, through the work of Levaditi, that the incubation at 37 C. of minced liver with atoxyl gives an active product in vitro. The fact has been observed also with tryparsamide but the exact nature of the product has not been elucidated.

(3) Particularly important is the fact that normal trypanosomes in contact with a serum medium of an arsenical trivalent derivate render it atoxic, evidently by fixation of the arsenical substance. Normal trypanosomes, placed in contact in vitro or in vivo with acriflavine, fix a revealing quantity of the product. The fact becomes still more significant by the following verification: chemoresistant trypanosomes do not themselves fix the aforementioned substances. One notes also that normal trypanosomes after contact in vivo with certain chemotherapeutic products (B 205 especially, arsphenamine), cease to be infectious long before disappearing from the blood. These verifications all tend to show the fixation of the product on the body itself of the parasite and, consequently, the alteration of its functions. Certain authors have formulated in particular the blocking in the parasite of molecules with an SH link which are indispensable to the general metabolism and known to react easily to arsenic (glutathion, cystein).

Chemoresistance. This question is of great practical importance because a given strain of trypanosomes may not be sensitive to therapy active on the majority of strains of the same species. It is important to note that this resistance concerns a peculiar quality in trypanosomes, observable in experimental animals, and is not a matter of therapeutic failure with patients, the explanation for which could be different. In nature, one may isolate from man strains of variable sensitiveness to one drug or another. It is often impossible in this case to tell if it is a question of an acquired quality or one peculiarly inherent to the strain. Experimentally, one can more or less easily transform a normal strain into a resistant one by the following procedures: (a) Repeated subcurative doses given to the same animal at each relapse, and eventually to other subinoculated subjects, result in rendering the strain refractory to the maximum tolerated dosis of the product. This method is easily successful with arsenical pentavalents but not with potassium emetic or the Bayer 205. It gives, of course, trypanosomes antigenically different from the original strain (relapse trypanosomes adapted to the antibodies of the serum or, to use Ehrlich's term, "serum fast" trypanosomes). (b) During treatment and before the disappearance of parasites, these are passed on to another animal to be treated afterwards. In this case trypanosomes conserve their primitive antigenic properties. They have never been relapse parasites. (c) Repeated contacts in vitro with an active product followed by inoculation in animals (contact and inoculation alternated) have also provided a resistant strain.

Our current practice seems to indicate the eventual carrying out of the first method. Spontaneous mutations of resistance have also been observed in strains of trypanosomes maintained on untreated animals.

Properties of chemoresistant strains. This concerns stable mutation, persisting not only in mechanical passages, but also during the course of cyclic passages. (W. Yorke and colleagues, and Van Hoof and colleagues). One can understand that this last possibility constitutes a grave menace for our prophylactic system. In fact, in certain regions, the number of clinical cases of chemoresistance has appeared to be considerable. Specificity of resistance is not as certain as has been believed, and it has been proved that resistance to atoxyl is, in fact, a resistance to aromatic links and includes several aromatic compounds of arsenic and antimony, and even trypaflavine (nonarsenical). This recalls the concept of the haptophorous group, fixing the toxophorous group on the parasite. The resistance would establish itself vis à vis to the former.

Contrary to what was hitherto believed, it has been proved that resistance is independent from the species of host. As to the mechanism, it is observed that resistant trypanosomes also show much less sensibility in vitro probably because of less permeability toward the product. As we have already said, this impermeability has been noted experimentally (absence of fixation of the active product). To quote Ehrlich again, one would say that the resisting trypanosomes have lost their chemoceptor for a given substance.

Diagnosis of chemoresistance. A patient who, during the course of treatment, or immediately after a normal treatment, still presents trypanosomes in the blood, is probably a carrier of a drug fast strain. This fact can be confirmed only if, transported to the guinea pig or the monkey, the strain shows itself abnormally resistant to the given product. There exist different degrees of resistance for each product.

Treatment of chemoresistance. One must obviously verify for use those products which are still active on the strain. The Bayer 205, antimonials, diamidines will frequently constitute the last resource.

Prophylaxis of chemoresistance. It seems desirable to use strong doses in the beginning, to have recourse to combined therapeutic and, in particular, to the use of B 205 at the beginning of the treatment. This product develops chemoresistant strains with difficulty.

PROPHYLAXIS

Prophylaxis against the disease involves both measures taken against the fly and measures applicable to the healthy or diseased man.

1. *Against glossines.*

(a) Clearing of the river borders so as to suppress deep continued shade and underbrush (large isolated trees may be maintained). This work must take place from 500 to 1,000 meters up and down stream. The final result will be the best judge: complete disappearance of tsetse flies must be achieved. This method applies to all man's settlements, bridges, roads, etc.

(b) Capture of flies by "fly boys," a method difficult to apply.

(c) Capture of flies in traps of the Harris type. These traps, more or less imitating a cow, made of canvas, opened at the top but without exit, are placed in suitable sites.

(d) Protection of game in reserves or national parks and its elimination near human habitations.

(e) Monthly dipping of cattle in a water suspension of DDT.

2. *Measures applying to human reservoirs.*

(a) Suppression of contact between man and fly. Sick people must be isolated in fly-proof places.

(b) Prohibition of traveling into a zone of glossines by infected subjects. Travelers must therefore be examined, and a travel ticket should not be delivered except on production of a medical passport, certifying absence of disease, or a certificate stating that the subject has been treated and presents no danger.

(c) Diagnosis and early treatment of all cases. This supposes, as previously stated, a nominative and family census of all the population (repeated every 6 months at least) and the treatment of infected subjects with verification of results in order to trace chemoresistance.

3. *Measures concerning the healthy population.*

(a) Establishment of the entire population in localities free from glossines. This measure, difficult to apply, has been used notably at Lake Edward (Belgian Congo), etc.

(b) Prophylactic injections of healthy subjects with Bayer 205 (to be repeated every 3 months) or with pentamidine (to be repeated every 6 months). Extensive trials made in the Congo with Bayer 205 appear successful. Pentamidine has been shown experimentally to be even more active: several volunteers who received 2 to 3 mg. per Kg. of body weight, developed a ten to twelve months' resistance against bites of infected tsetse flies. During recent experiments in the Congo, administration of 5 mg. per Kg. of isethionate of propamidine to thousands of individuals has not caused any important or lasting accidents. Nevertheless, pregnancy is a contraindication: $^1/_2$ to 2 hours after injection pains and uterine contractions are felt, and out of 14 pregnant women, 4 showed incidents, of which 2 were followed by miscarriage. This effect is manifested when 2.5 mg. per Kg. is exceeded. Protection remained effective for 8,000 natives over a period of eighteen months, after re-injection at the sixth month (Eeraerts-Claessens).

The practical use of these methods is still under investigation, but appears favorable. Rightly they have been objected to as involving toxic risks. Lester admits one death for the first 2,000 injections of 1 Gm. of antrypol. This risk, such as it is, cannot be run repeatedly. It is possible that diamidine will be preferred to B 205 in which case there will be a possibility of intramuscular injections with less toxicity. Chemoprophylaxis could also make certain infections cryptic at their early stage.

2. AMERICAN TRYPANOSOMIASIS. CHAGAS' DISEASE

Definition: Acute or chronic general infection caused by *Trypanosoma cruzi (Schizotrypanum cruzi)*, Chagas, 1909, and transmitted by Reduvide insects especially of the *Panstrongylus* (*Triatoma*) genus. Acute symptoms are of infectious type; chronic symptoms are in relation to the parasites' intracellular localization.

HISTORY

In 1909 Chagas first discovered the parasite in the Triatoma's intestine, then in monkey blood infected by these insects, and again in children. In 1916 he described the disease in man. The study of the Argentine focus (Romaña, Mazza and colleagues) is more recent.

GEOGRAPHIC DISTRIBUTION

Since the first discoveries made in Brazil (State of Minas Geraes) the disease has been gradually discovered in nearly all South American states, and in certain states of Central America (Panama, Guatemala, Mexico). The vectors and even the flagellate are found in the U.S.A., but to the present time not the disease. This has never spread greatly and in most countries known cases amount to a few dozen, at the most a few hundred.

ETIOLOGY

Trypanosoma cruzi are never abundant in patients' blood. The parasite is usually met only during feverish attacks. It presents itself under two forms, one narrow and about 20 microns long, the other shorter and broader. On fixed and colored smears, *Trypanosoma cruzi* very often follows the design of a Chinese bridge (forms like C or V). The kinetoplast is subterminal and relatively large which makes it distinct from other trypanosomes. The free flagellum is often torn off on the smears.

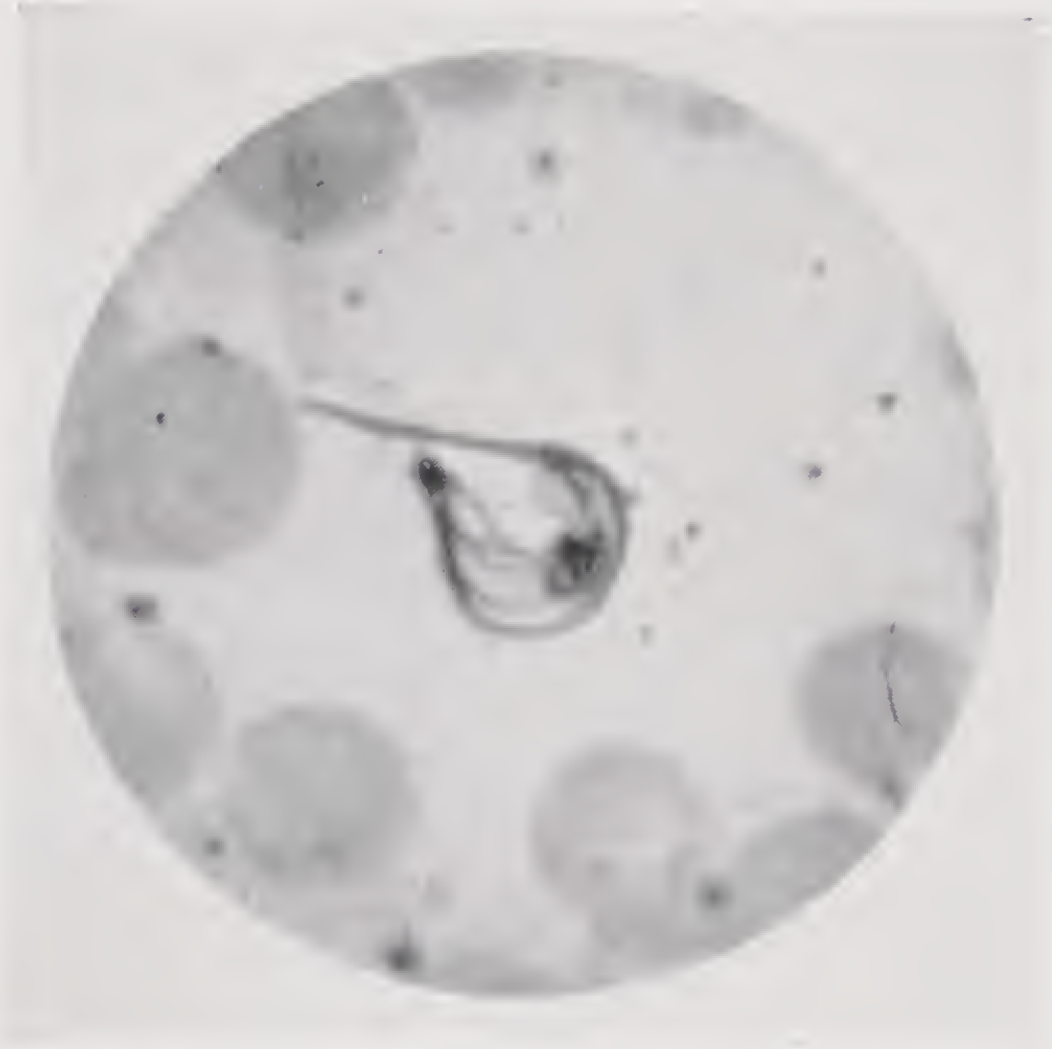

FIG. 11. TRYPANOSOMA CRUZI, IN THE BLOOD
Coll. Tropical Institute, Antwerp

In tissues (cardiac and striated muscles and more rarely the thyroid gland and brain) the trypanosomes penetrate the cells. There they lose their flagellum, become round and take the form called "Leishmania," round or oval, measuring from 3 to 5 microns in diameter. A spheric nucleus and a rodlike kinetoplast are easily found. These Leishmania forms, adapted to intracellular life, multiply themselves by repeated binary division.* They fill the parasited cells rapidly, distend them, and constitute cysts, sometimes enormous, causing mechanical troubles in the tissues.

These parasited cells or cysts tear and release Leishmania forms which in a liquid medium (interstitial or plasma) grow longer and produce a flagellum out of the kinetoplast. Evolution then continues in Leptomonas forms (kinetoplast at the anterior tip of body without undulative membrane), Crithidia (kinetoplast near the nucleus, undulant membrane caused by the kinetoplast drawing the flagellum to the center of the body), and Trypanosoma or infecting blood form (posterior kinetoplast and undulant membrane over nearly the whole body). Culture of *Trypanosoma cruzi* is easily made on mediums containing blood or the essential blood constituents. In culture, one notes a phenomenon of involution and a return to Crithidia and Leptomonas forms.

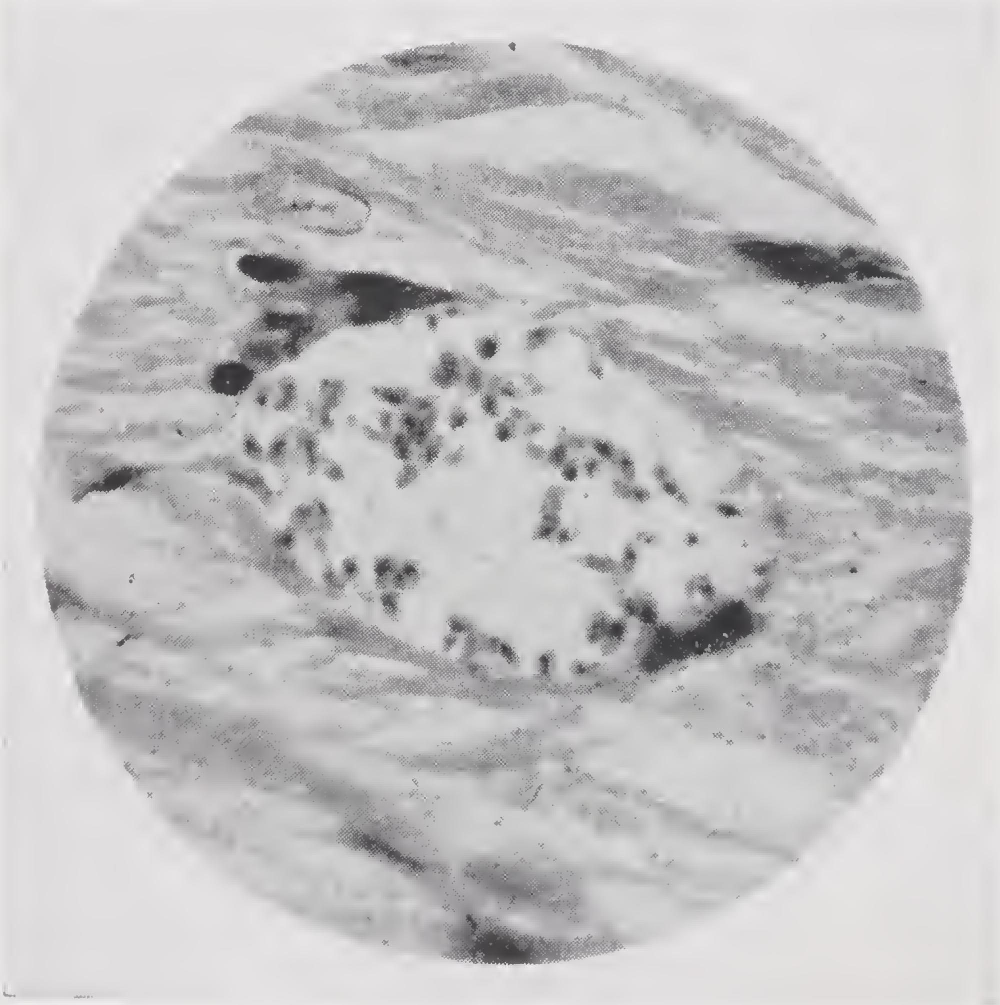

FIG. 12. TRYPANOSOMA CRUZI, IN THE TISSUES: LEISHMANOID FORMS
Coll. Tropical Institute, Antwerp

TRANSMISSION

The classic intermediate host of Chagas' disease belongs to the Reduviidae family. The genus *Panstrongylus* (formerly called *Triatoma*) alone contains nearly twenty species which show themselves infected in nature: notably *P. megistus* (the "barbeiro") in Brazil, *P. infestans* (the "unchusa") in Argentina and Uruguay, *P. geniculatus* in Panama, *P. dimidiatus* in Guatemala, and *P. protractus* in California. Natural infections have been met with in numerous Arthropodes belonging to the genera *Rhodnius*, *Eratyrus*, and *Eutriatoma*. Experimentally infection may be transmitted to bed bugs (*Cimex lectularis* and *Cimex rotundatus*) and to numerous ticks (*Ornithodorus moubata*, *Rhipicephalus sanguineus*).

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* The name Schizotrypanum is therefore not correct.

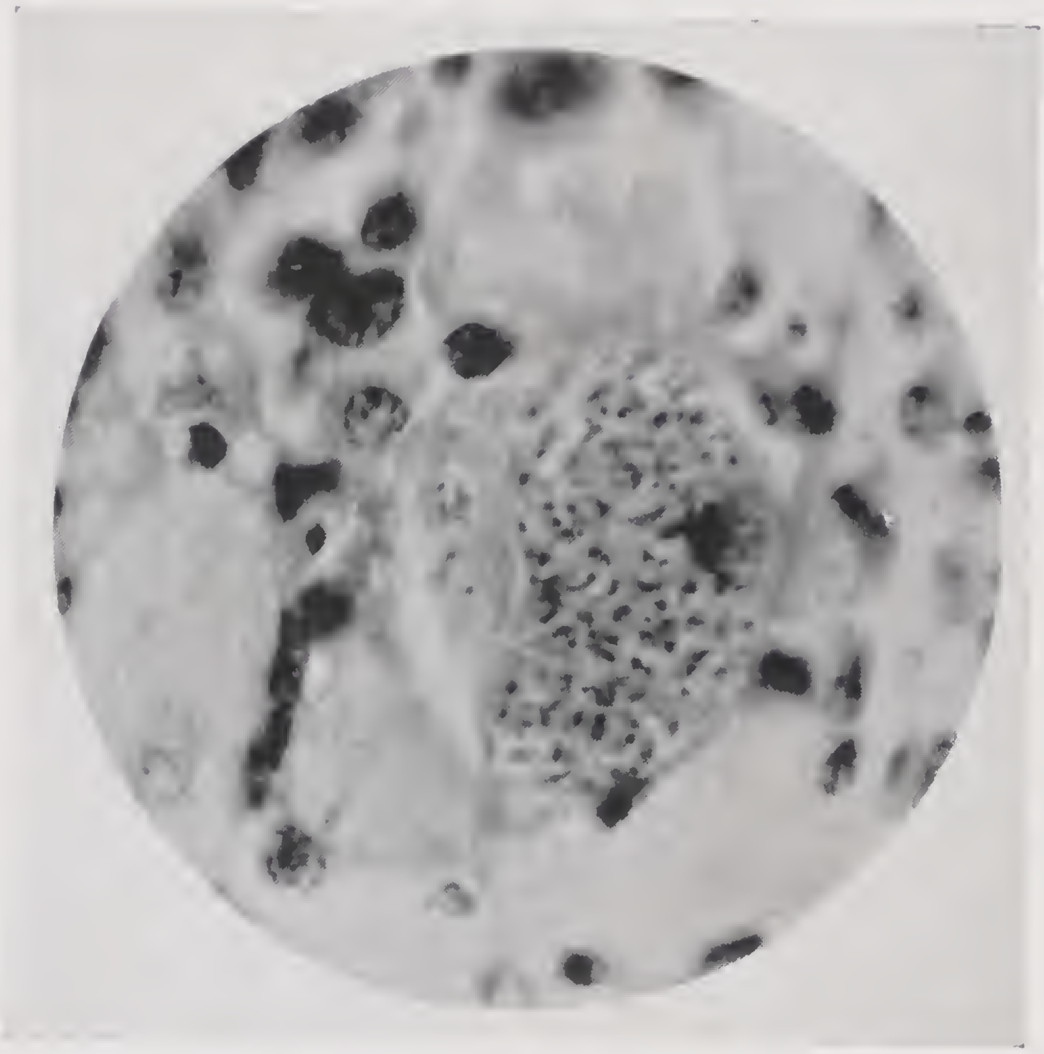

FIG. 13. TRYPANOSOMA CRUZI, IN THE TISSUES: LEISHMANOID FORMS

The triatomes (*Panstrongylus*) are large sized arthropodes nearly 2 cm. long. The larvae and nymphs, almost adult sized, are apterous. Adults have wings but make only brief flights. They hide in cracks and interstices of the ground, walls, and roof during the day, and at night feed on sleepers, often on the face (kissing bug), on domestic and wild animals, especially the armadillos (*Dasypus*), opossums (*Didelphis*), and certain monkeys (*Chrysothrix sciureus* in Brazil). These animals constitute an important reservoir of virus. The biting of a sleeping man by triatomes is painless and often causes no local irritation. Adults, nymphs, and larvae are equally susceptible and are good transmitters. In the digestive tube of these arthropodes, ingested trypanosomes multiply and regress to the Crithidia form. In the terminal part of the intestine, infectious trypanosomes appear 8 to 10 days after the infecting meal. These infectious trypanosomes, called "metacyclic," are expelled with the excrements. The infection can be hereditary in triatomes. Nevertheless one must consider the possibility of young triatomes infecting themselves by biting the distended abdomen of infected adult triatomes. An infected triatome remains so for two years.

Transmission to man is essentially made by contamination at the bite or on skin scratched and then infected by infectious excrements of triatomes. Infection by regurgitation during the biting occurs only occasionally. The deposit of infecting matter on mucous membranes and on the conjunctiva also brings about infection. Transmission by coition and breast feeding has been considered possible in human subjects.

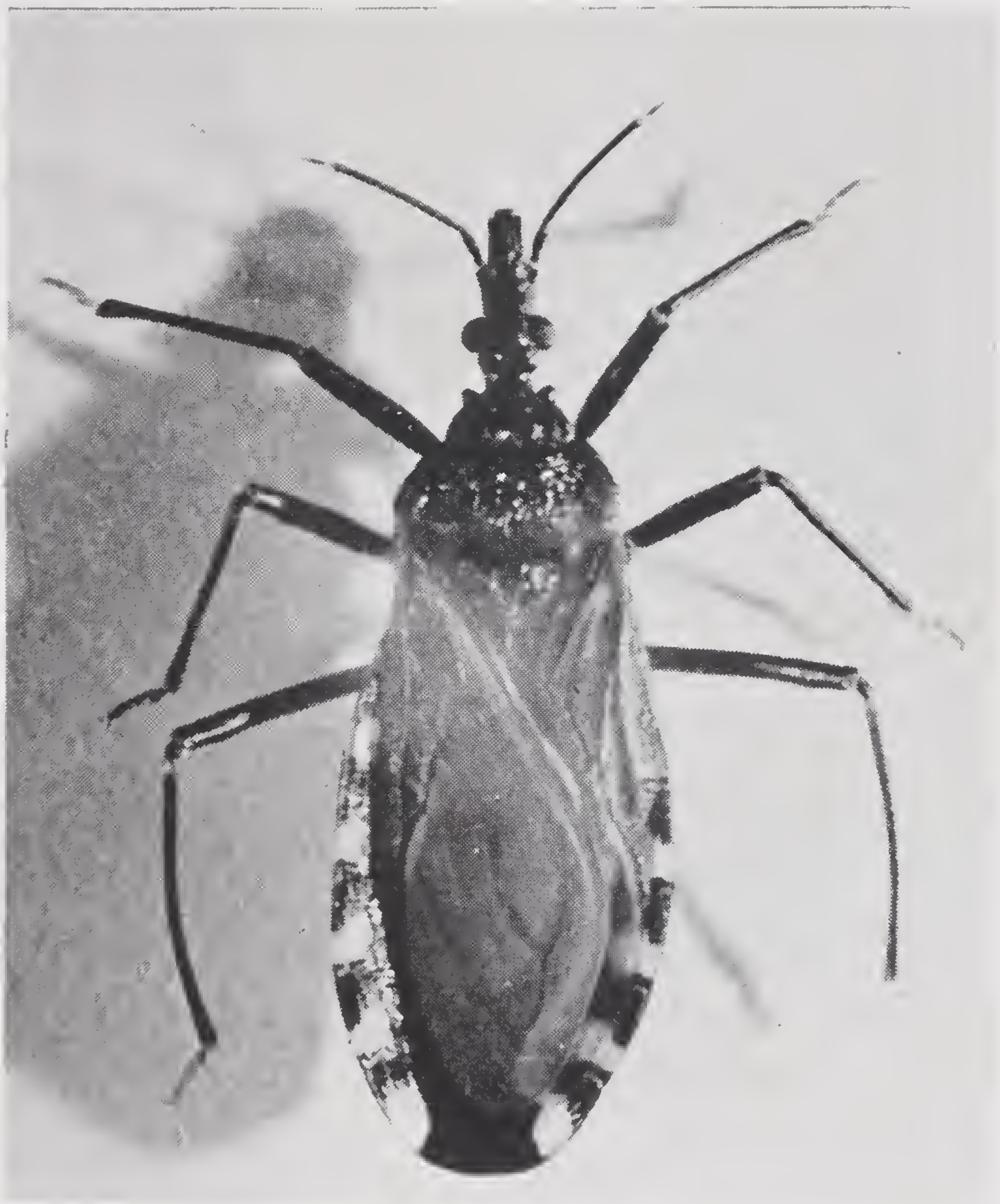

FIG. 14. TRIATOMA (PANSTRONGYLUS) MEGISTA
Phot. G. Boné, Tropical Institute, Antwerp

It is surprising to observe how few individuals are attacked by Chagas' disease in spite of the wide geographic distribution and the abundance of possible vectors. It would seem that *Trypanosoma cruzi* is a natural parasite of armadillos, opossums, and perhaps monkeys, and an accidental one in man. One should remember the sedentary nature of triatomes which do not leave the burrows, stables, and houses so long as these are occupied by the wild and domestic animals or man on which they feed.

PATHOLOGY

The tissular lesions are due to the mechanical and toxic actions of the parasite. Frequently there is no inflammatory reaction around undamaged parasitized cells. This is probably not the case when the cells are ruptured. The alterations of the parenchyma seem to be related chiefly to the toxic action of the parasites. Macroscopically, edema, serous effusions, adenopathia, and cardiac dilatation with petechiae are observed. The spleen is moderately hypertrophied. The liver is swollen and may present fatty degeneration. In the lungs edema and congestion are encountered.

The microscopic pathology has been particularly well described in the myocardium: diffuse, exudative myocarditis with degeneracy of the fibers, presence of intracellular parasites. This acute stage is followed by chronic lesions of the fibers. In the brain which is less heavily infected than the heart, parasites may be observed in the neurones or in the glial cells, with here or there small inflammatory nodules.

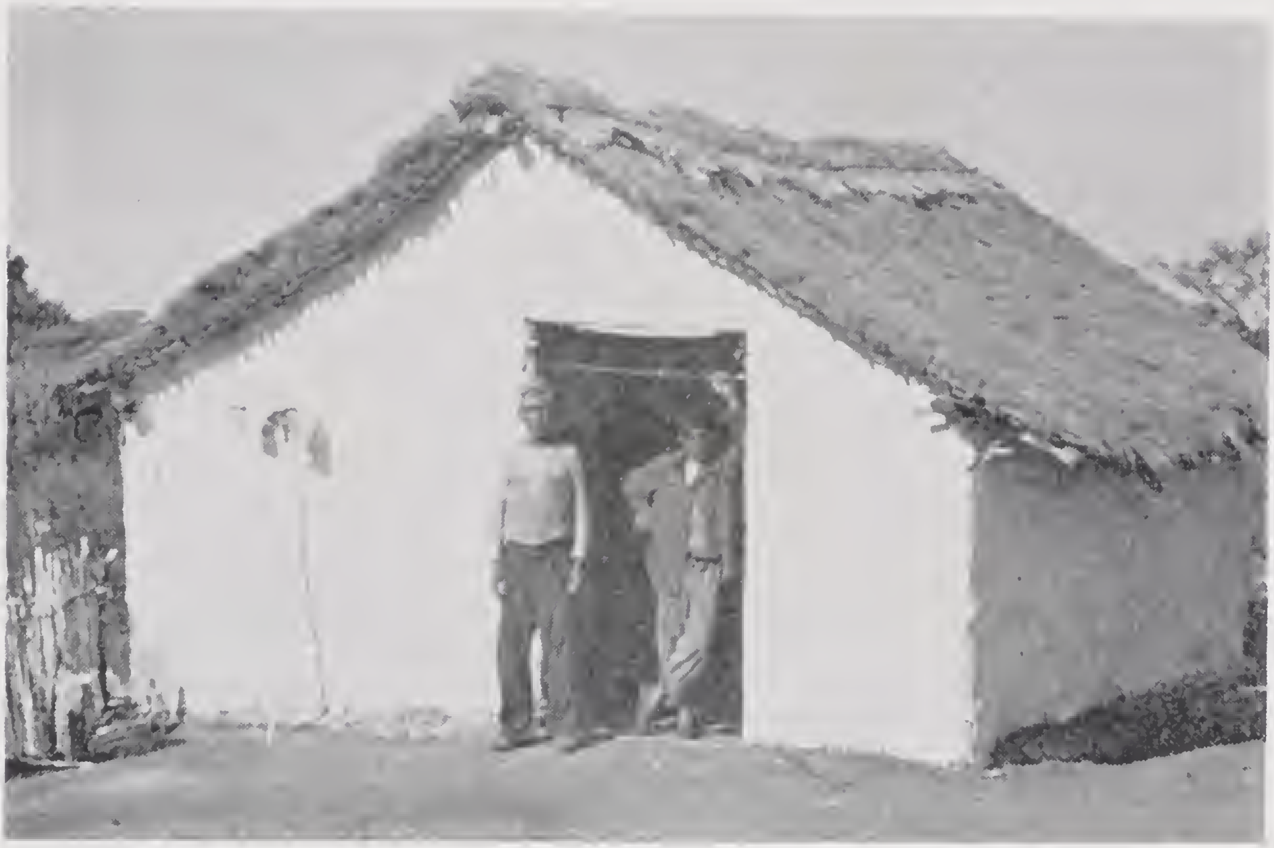

Fig. 15. South American Dwelling
Typical as a refuge for "vinchucas" or Triatomas (courtesy Dr. Romaña)

SYMPTOMATOLOGY

Incubation is from ten to thirty days. The acute form has been observed principally in children, with irregular fever, anemia, nonsuppurative adenopathy, swelling of the liver and spleen, firm and elastic edema of the facial region, sometimes general edema, tachycardia even without fever, and hypotension. This form evolves as an acute infection which can end by fatal encephalitis. Attacks of thyroiditis have been observed. This serious form has been seen especially in Brazil. In central America and in Argentina milder forms are usually seen, even in children.

It is in Argentina that the Romaña sign has been described, corresponding to a primary lesion: swelling of eyelids, dacryo-adenitis, conjunctivitis and lymph node reaction. The phenomena are in relation with the parasites' passage across the conjunctiva because of the frequency of facial bites. The passage through the skin determines a local lesion, resembling somewhat a nonevolutive boil, accompanied by ganglionic reaction (Mazza). In Argentina, cutaneous nodular lesions have been observed. Infectious phenomena are sometimes very discrete. With adults the disease evolves in a chronic manner, such as was the case especially during different experimental inoculations. This form, observed also among children cured of the acute phase, has a very confused symptomatology.

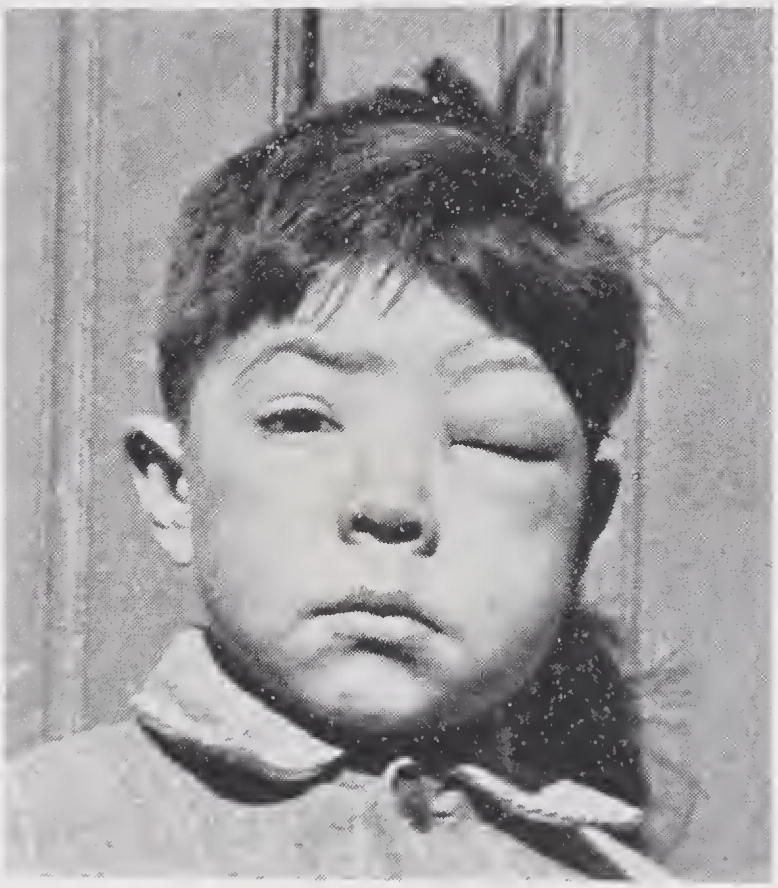

FIG. 16. ACUTE FORM OF CHAGAS DISEASE: ROMANA'S SIGN
Courtesy of Dr. Romaña

Chagas recognized a *goitrous* form (parasitic thyroiditis). This might well be the simple goiter so common in certain countries. The *nervous* form presents clinical manifestations of great variety. Although the existence of lesions caused by the trypanosome seems established, it is possible that these have frequently been confused with cretinism or other nervous diseases.

The *cardiac* form, attributable to sclerous lesions in the myocardium with various clinical phenomena, appears to be the most definitely established of these forms and is the cause of many sudden deaths observed in these regions (myocarditis, extrasystoles, arythmia, asystolia, bradycardia, heart block, etc.).

Alterations of the electrocardiogram and an enlargement of the cardiac area shown by x-rays are frequent. These lesions are commonly seen in young subjects (Dias and colleagues).

PROGNOSIS

Prognosis varies according to age and country. In Brazil, mortality of nearly 50 per cent has been noted in infantile acute forms. Mortality in Argentina does not exceed 6 per cent. With adults, the prognosis quoad vitam is favorable.

DIAGNOSIS

Considering the uncertainty of clinical manifestations one must have recourse to systematic blood examination in endemic countries. Generally, in place of direct examination (above all, useful in cases of fever), inoculation of guinea pigs is preferable (5 cc.), or hemoculture. The Leishmania forms may be found in the lymph node of the primary complex or in the bone marrow (Dias and colleagues, 1945). Finally one should note the "xenodiagnostic," according to Brumpt, which consists in having the patient bitten by cultivated reduvides, then investigating for intestinal infection. Direct research concerning parasites in the blood is difficult in chronic cases. It is negative in secondary lymph nodes.

Serology appears also to offer possibilities: tests of Guerrero and Machado, Kelser, Romaña and Dias, Davis (fixation of the complement in presence of a specific antigen). One must exclude the Leishmaniases.

TREATMENT

It is curious to note that the usual trypanocidal drugs are inactive here. One might consider the intracellular seat and especially the interior of the sarcolemma, although the location in the mesenchymal cells does not protect the Leishmanias.

Two substances prepared by the Bayer firm, 7602 related to Surfene, and 9756 which is an arsenical, may have a certain curative action but to date definite therapeutic results have not been reported. Penicillin is under trial (Mazza).

PROPHYLAXIS

Dwellings of beaten earth or adobe with thatched roofs should be avoided. Bed mosquito nets protect the sleeper against the triatome bites. Infected domestic animals (cats and dogs) should be killed. Houses which have lodged a case of Chagas' disease must be destroyed as well as adjoining stables or dwellings sheltering beasts and people. New houses must have foundations which will prevent armadillos burrowing beneath them.

3. VISCERAL LEISHMANIASIS*

(INDIAN KALA-AZAR—INFANTILE LEISHMANIASIS)

Definition. Endemic disease caused by *Leishmania donovani* and clinically characterized by prolonged fever, hepatosplenomegaly and serious anemias. Transmission is due to Phlebotomes.

HISTORY

An ill-defined febrile syndrome has been known in Assam since 1882 and called Kala-azar or Black Fever. It is possible that the same disease was prevalent before that period in Bengal, but the epidemic in Assam was especially deadly. Rogers in 1896 considered it a grave form of malaria. Manson put it down to a trypanosomiasis. In 1903 Leishman discovered the parasite. The clinical knowledge of the "ponos" raging in the Mediterranean islands is ancient.

GEOGRAPHIC DISTRIBUTION

The disease has been noted in the East Indies (Assam, Bengal, Madras), North China and Manchuria, Asia Minor and Central Asia, the Mediterranean area (Sicily, French coast, Greek Islands), North Africa, the Anglo-Egyptian Soudan and Abyssinia. It is unknown in the Congo. During the past few years (1934–1937) viscerotomy has brought to knowledge cases in Brazil and Argentina.

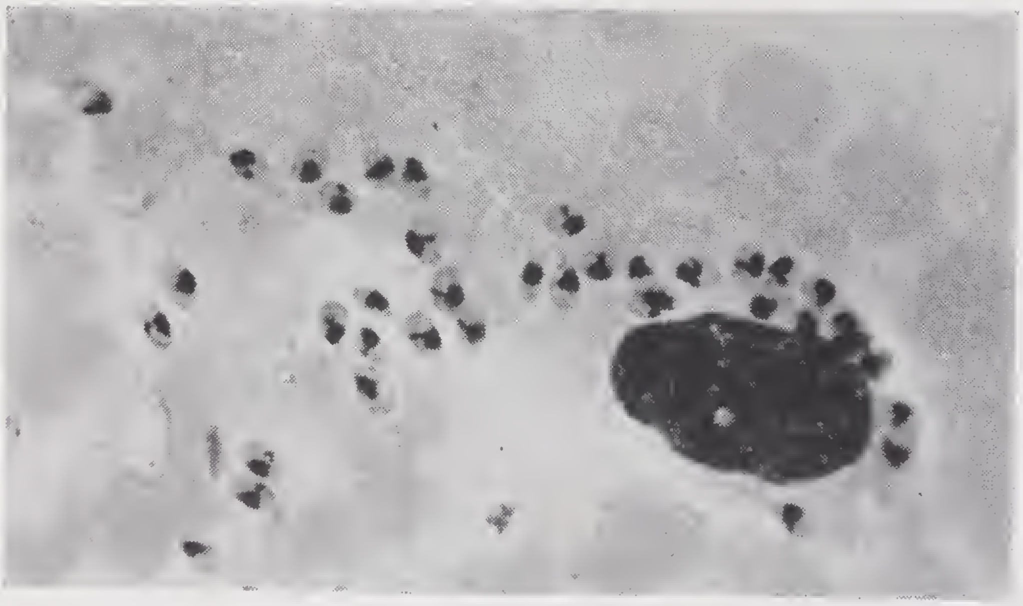

FIG. 17. LEISHMANIA DONOVANI, INTRACELLULAR AND EXTRACELLULAR FORMS
Courtesy of Dr. Shortt

ETIOLOGY

Leishmania donovani (Protozoon, family *Trypanosomidae*, genus *Leishmania*) was called to Leishman's attention for the first time in 1903 in the splenic pulp of an Indian soldier, who died of "dum-dum" fever. At the same time Leishman discovered an analogy between this parasite and the trypanosomes of the rat. In 1903 Donovan discovered the same parasites in the splenic smears of sufferers of the same fever. Laveran and Mesnil interpreted the parasites of Donovan's preparations as piroplasmas (*Piroplasma donovani*) while Ross considered them to belong to a new genus of Sporozoa, *Leishmania donovani* (November 1903).

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* French: Leishmaniose viscérale. German: Viszerale Leishmaniase.

These round or oval parasites measure 2–4 microns. They possess a nucleus, a rodlike kinetoplast and often a very thin residue of flagellum joining the kinetoplast to the edge of the cytoplasm. In microscopic sections the Leishmania present themselves in groups inside the cells, particularly in the macrophages. In smears they often become extracellular and then their organization is much more clearly revealed.

In 1904 Rogers in India obtained the culture of *Leishmania donovani* and demonstrated at the same time that the parasite was a flagellate belonging to the family *Trypanosomidae.* Inoculating the product of splenic puncture from a case of Kala-azar into a culture medium (citrated saline, between 20 and 22 C.) he obtained after three days numerous elongated flagellates of the *Leptomonas* type with an anterior flagellum and kinetoplast.

There is no difficulty in the culture of *Leishmania,* in the absence of bacterial contamination, on citrated blood or on the blood medium called Novy Neal Nicolle ("N.N.N."), even better on glucose "N.N.N." (Nöller). Ascorbic acid, hematine, and an unknown factor present in the serum are indispensable to the growth of the *Leishmania* in cultures. They succeed equally well on embryonated chick eggs.

The two species, *Leishmania infantum* and *Leishmania chagasi,* which appear respectively in the Mediterranean area and Brazil, as well as the species *Leishmania caninum* of the dog, are at present considered as varieties of the *Leishmania donovani.*

Man and dog, the latter only in certain regions (see prophylaxis), are the principal reservoirs.

TRANSMISSION

Transmission is by a small diptera: the Phlebotomus. Several species intervene, notably: *Phlebotomus perniciosus,* in Italy; *P. argentipes,* in India; *P. chinensis* and *sergenti, var. mongolicus* in China; *P. perniciosus,* in the Soudan; *P. intermedius,* in Brazil.

The Phlebotomes are small insects with arched thorax and lanceolated wings. These, as well as the feet and the whole body, are covered with long hairs. They are able to fly only a short distance. The females alone feed on blood sometimes of superior, at other times inferior Vertebrates. The females drink their fill in the evening or at night and are found in daytime in dark places. Certain kinds take only one meal of blood followed by the laying of eggs and death. Other species suck blood several times, laying eggs after each meal. Long and oval eggs are laid in groups of about fifty in cracks and crevices of damp dark places. The larvae are hatched after ten days and live on organic waste. The adults come to light after four larval sheds and a nymphal stage, all this lasting about a month.

The *Leishmania* are transformed in the stomach of the Phlebotomes into *Leptomonas*, the multiplying form. Elongated, metacyclic shapes line the walls of the pharynx and cause a blocking of the same (as in plague for certain species of fleas). Transmission to a sensitive man or animal takes place through regurgitation before the bite, as the aspiration of blood by the infected Phlebotomus is possible only after the liberation of the pharynx and the injection of infecting Leptomonas forms. Phlebotomes caught in houses harboring a case of kala-azar are most frequently infected. Experimental transmission succeeds easiest with the China hamster (*Cricetulus griseus*). Transmission has also been performed recently (1942) on man by the bite of *Phlebotomus argentipes* previously infected on patients. Probably direct transmission also occurs. The *Leishmania donovani* are found in the urine, stools, and nasal mucus. Susceptible animals (mouse, hamster, monkey) have been infected by ingestion of human products or crushed phlebotomes.

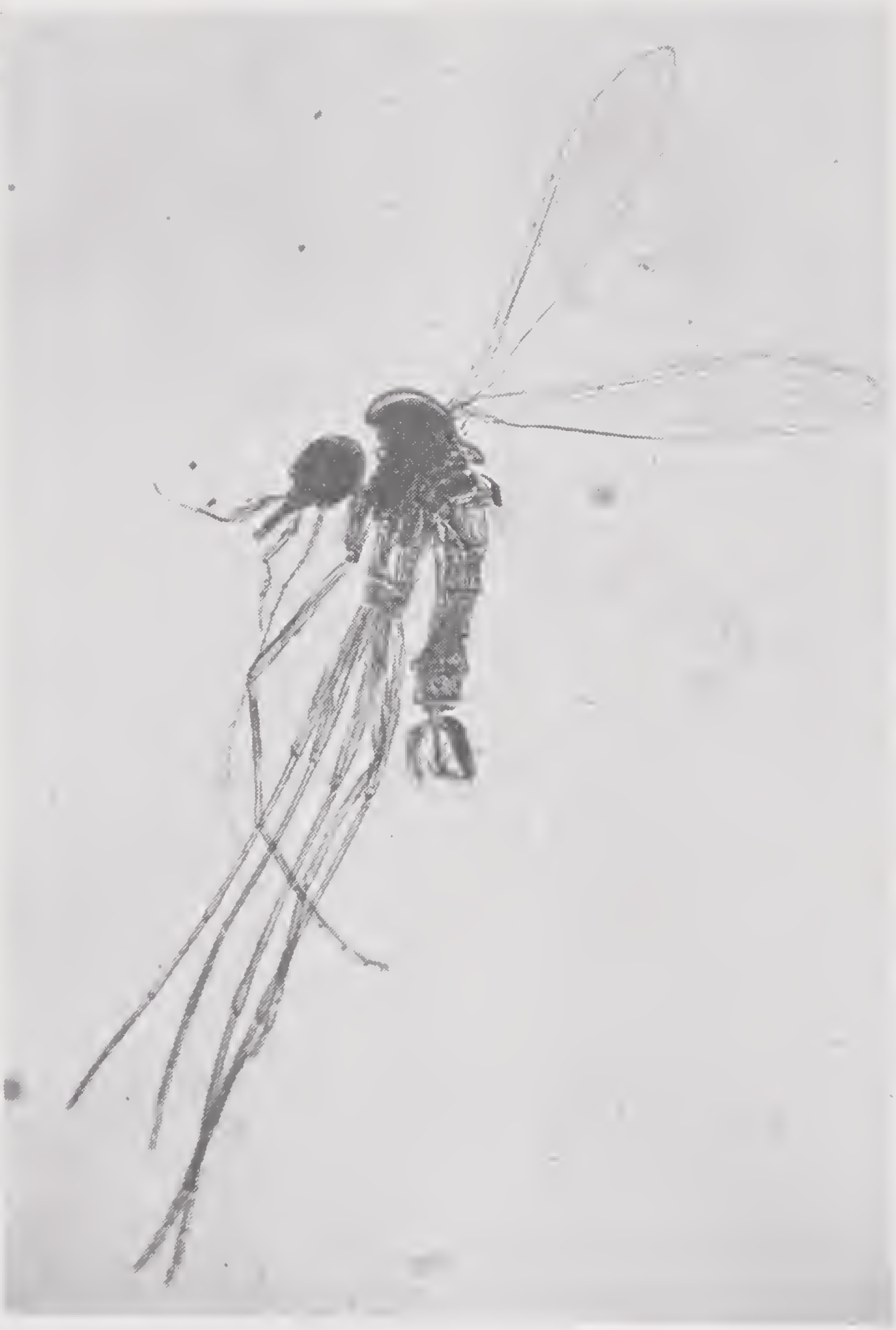

Fig. 18. Phlebotomus papatasii
Phot. R. Resseler, Tropical Institute, Antwerp

Infection from man to man seems chiefly possible by nasal mucus. Leishmania have been found infective after 72 hours in milk and food. Congenital transmission from mother to child has been described.

PATHOLOGY

Leishmania are parasites of the reticulo-endothelial system and they produce a hyperplasia of its elements. Macroscopically, besides cachexia one notices splenomegaly often associated with hepatomegaly. The spleen is always voluminous (up to 1,000 and even 3,000 Gm.), sometimes enormous and soft in acute cases and more or less fibrous in long standing cases, with infarctus and disappearance of the Malpighian bodies. The liver is often large, congested, or fattish. The bone marrow is red even in the long bones; under the microscope one observes the multiplication of the spleen endothelial cells in the sinuses and pulps with necrotic foci. The hyperplasis of the Küpfer cells of the liver crush the hepatic cells, and less evident is the multiplying of reticular cells of the ganglions.

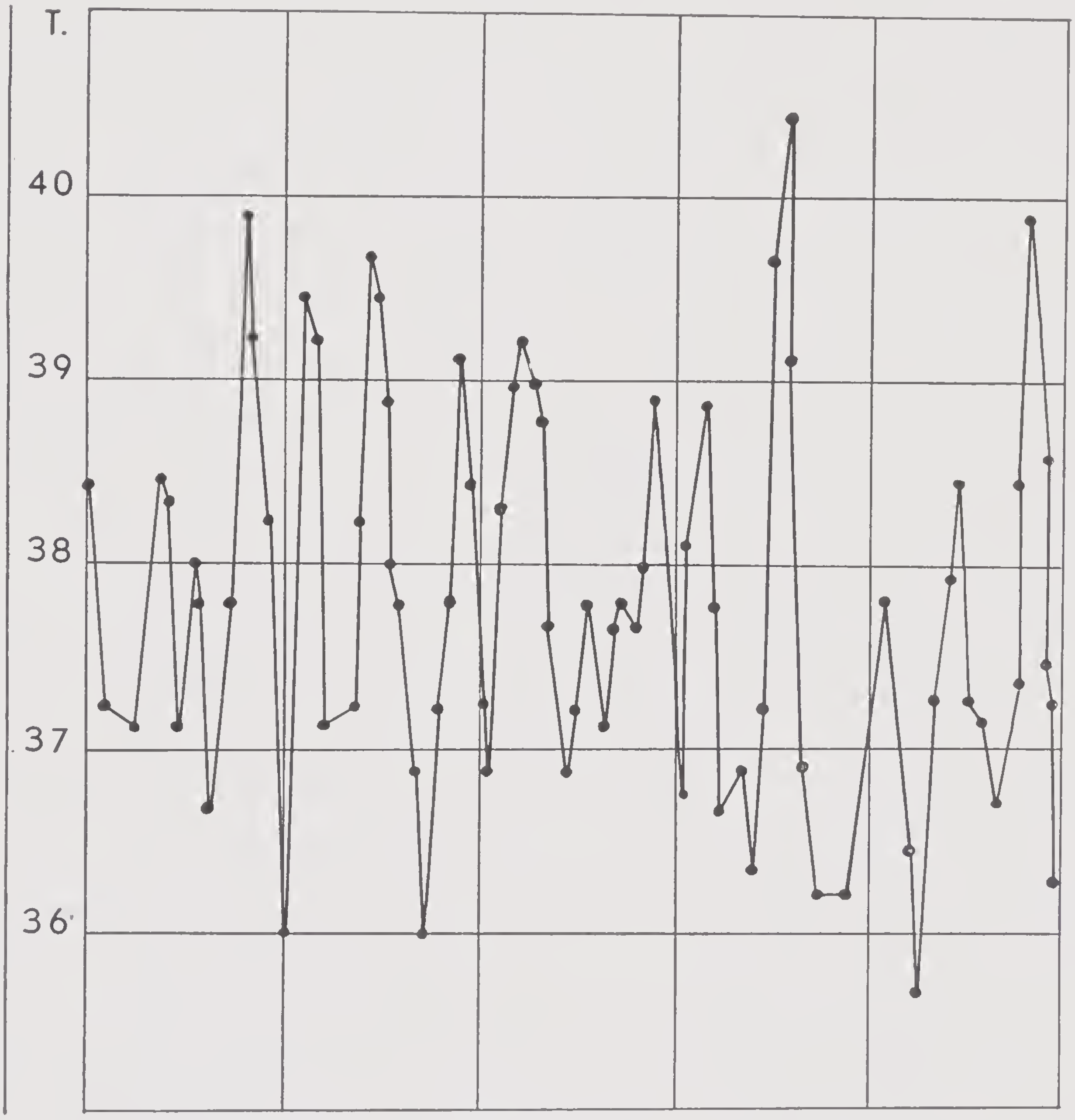

Chart 4. Kala-azar. Small part of the curve (Col. Shortt)

In the liver and more especially in the spleen the cells are crammed with parasites. It is also possible to find macrophages with parasites in other parts of the body (intestine, bone marrow) and also in the skin in case of nodular lesions. Skin macules are generally exempt from parasites.

In the intestines there exist on the level of parasitized villosities, small ulcerations which secondary infections can enlarge.

The infiltration observed in different organs is composed of plasmocytes and lymphocytes. No granulocytes are found and suppuration never occurs.

SYMPTOMATOLOGY

After an ill defined and at the same time very variable incubation (from several days up to several months), the first stage is sometimes acute, resembling malaria, at other times progressive like typhoid fever, or even very torpid. Fever is the most constant symptom during the first period of the disease. It is always of considerable duration with intervening apyretic periods. The fever shows a remittent curve with most typically, although not always, two remissions a day. The temperature should be taken every three to four hours. Functional phenomena associated with this state are often discrete and the patient may move about in spite of being feverish. Adenopathy is frequent. The subsequent cachectic period also shows emaciation, resorption of the muscles, dry, scaly and dark skin, and visceral symptoms; a sometimes painful splenomegaly (among children), hepatomegaly, more rarely ascitis and edema. The condition can be aggravated by stomatitis, noma, dyspepsia, and dysentery which is sometimes due to intestinal localizations of Leishmanias, but more frequently to added infections (Shigella, Entameba), broncho-pneumonia, and different kinds of hemorrhage. A more or less clearly defined normochromic anemia is a constant though not very early sign of kala-azar. Leukopenia is particularly striking with granulopenia and monocytosis.

In kala-azar a marked reduction of the serum-albumin is found, together with an increase of the euglobuline and an inversion of the albumin globulin ratio.

Infantile Leishmaniasis also appears as a fever with anemia and splenomegaly ending in death after about a year.

Dermal Leishmaniasis

Cutaneous phenomena are observed occasionally in kala-azar, especially one or two years after an apparently successful treatment. They start with small depigmentations of the face, hard to diagnose, for they contain no parasites. Subsequently firm nonulcerating nodules develop in the face, which can be mistaken for leprosy or xanthoma. These nodules contain parasites.

PROGNOSIS

Prognosis should always be reserved, as up to 90 per cent deaths have occurred. Yet there are comparatively light forms. Other more serious febrile cases decline rapidly. The usual chronic form ends in death from complications.

DIAGNOSIS

An early clinical diagnosis may be difficult. Armstrong (1945) has observed two cases among Europeans where the disease remained latent for months. In one of the cases there was splenomegaly. In other Europeans in the Mediterranean basin, cervical adenopathy constituted the only symptom.

The very slight "toxic" character of the fever will attract attention and will hasten an examination of the bone marrow (Lowe, 1944). The triad—prolonged fever, hepatosplenomegaly, and anemia—should lead to the diagnosis, as well as the cachectic state, especially with hemorrhage, dysentery, etc.

Mention has been made of a remission of fever twice a day, but this symptom is neither constant nor continuous. Among diseases to be considered for differential diagnosis, malaria should be quoted, as well as certain forms of tuberculosis, cryptogenetic splenomegalies, schistosomiasis, hepatic cirrhosis, leukemias, etc.

Parasitologic diagnosis is essential, all the more so as the treatment is not without risk and would obscure the problem.

The parasite is made a subject for research:

1. *In the spleen.* (Puncture when firm, rather than soft, as the latter is subject to bleeding.) First verify the coagulability of the blood; give calcium; use a fine and dry needle and a dry syringe. An assistant fastens down the spleen, the needle pierces the abdominal wall, then during apnea penetrates into the spleen. Rapid suction brings up a small quantity of splenic tissue. (Blood is not favorable.) After the puncture, rest in bed, compressed bandages and supervision for twenty-four hours are indicated.
2. *In the liver.* This is a less certain method but probably of easier access. Shortt (1947), after several thousand investigations, considers the puncture of both viscera as harmless. (Only applicable to enlarged livers.)
3. *In the bone marrow* (sternum, iliac crest). This harmless method is attaining a consistently wider use, and will probably take the place of visceral punctures.
4. *In the lymph nodes.* Very uncertain (relative scarcity of parasites).
5. *In cutaneous nodules*, or sometimes in apparently healthy skin and also nasal cavity.
6. *In the blood.* Examination of the leukocytic layer may be positive. The culture is more certain although the development is slow (10 to 20 days).

Serology. The test with formol, without being entirely specific, is useful. *Technic:* To 1 cc. of clear serum is added one drop of formol at the beginning. A white coagulation which turns dim in less than twenty minutes is considered as characteristic of kala-azar (schistosomiasis may produce the same appearance, but is easy to eliminate). The gelifications due to other diseases are not opaque. The serum deviates the complement in the presence of an antigen extracted from acid resistant bacilli (Witebski, Klingenstein, and Kuhn's antigen). Tuberculosis and grave leprosy are causes of error. The method has a 93 to 97 per cent efficiency.

TREATMENT

In 1912 Vianna introduced tartar emetic into treatment of the American muco-cutaneous Leishmaniasis. Caronia and Di Cristina in Italy and, at about the same time, Rogers and Muir, in India, made use of the same substance in kala-azar. The tartar emetic is prescribed in the same way as for sleeping sickness, while striving to attain a larger total dose (up to 2.5 Gm.). The objections to this have already been noted. Attention has been drawn to the frequency of pneumonia during the treatment. Later, pentavalent antimonial derivates were used: *Stibenyl* (formula of arsacetine where As is replaced by Sb), *Stibosan* (Stibenyl chlorated in meta position); both have now been abandoned.

Neostibosan (diethylamine p-amino-phenylstibinate, formula of atoxyl with an organic base replacing the sodium).

Solustibosan-Stibatine (antimonosodic gluconate).

Stiburée or Ureostibamine (derivate of p-amino-phenylstibinic acid), etc. These derivates, having about 30 per cent of pentavalent Sb, are decidedly less toxic than the emetic and capable of being injected into the muscles. They are naturally more expensive. A higher total dosage should be reached.

Neostibosan: 8 to 10 injections (intravenous or intramuscular):

of 200 to 300 and 450 mg. for an adult.
of 200 to 300 mg. between 10 and 15 years.
of 100 to 200 mg. between 5 and 9 years.
of 50 to 100 mg. between 2 and 4 years.
of 50 to 100 mg. for less than 2 years.

Solustibosan: Intravenous or intramuscular daily injections:

First dose: 2 to 6 cc. according to age.
Following doses: double the first dose.
Total dose for an adult: 100 to 120 cc.

According to Lowe, one should, with *Solustibosan-Stibatine*, reach 200 to 240 cc. for an adult, 150 to 200 cc. for an older child, and 100 to 125 cc. for a younger one.

In France, *Pentastib*, or the 2168 R. P. (N-methylglucamine antimoniate with 28.3 per cent of pentavalent Sb) has been used.

Diamidino-stilbene-Stilbamidine (M & B) or 4-4′-diamidinostilbene di-hydroxy-ethane-sulfonate (see treatment of sleeping sickness). In India and Sudan it is especially used in cases which do not respond to antimony. The dosage varies from between 1 to 3 mg. per Kg. of body weight, i.e., 50 to 150 mg. for adults (children in proportion can stand slightly more). Daily injections (veins and muscles) during a fortnight. Rest for a week followed by second course. Slow injection into the veins is required as well as adrenaline before or after an injection. Only solutions prepared just before use are to be utilized as light increases the toxicity. Death might occur as a result.

PROPHYLAXIS

Individual prophylaxis is hard to achieve. Mosquito nets, fine enough to keep out the phlebotomes, are very hot. Besides, the phlebotomes also bite people before sunset. Thorough ventilation of houses, as well as fumigations, are found efficacious. Certain repellents are recommended for use on the skin, e.g., oil of eucalyptus, turpentine, thymol at 5 per cent, and dimethylphthalate.

The most sensible measure is to fight the phlebotomes. Their haunts and egg-laying places are numerous: cellars, latrines, cracks in walls, manure, all kinds of rubbish and vegetable refuse, underneath decorative verandah plants, in heaps of stone and brick.

Very strict cleanliness is everywhere imperative where visceral Leishmaniasis is endemic. Spraying with paraffin has been used with certain favorable results. Better still is the use of modern insecticides (DDT) which will be much more efficacious as they hit not only the full grown insect, but also the larva.

In India and in Assam, isolation of the sick and those in contact with them, the treatment by antimonials of the former, and careful observation of the latter, combined with the destruction by fire of infected huts, have contributed greatly toward the decrease in infection. In Italy and Turkey reducing of the all too numerous dogs and destroying sick animals has proved efficacious. The dog seems to be the main reservoir of virus, at any rate in certain regions: Mediterranean area, South America, China. In India dogs do not show natural infection, yet they are experimentally sensitive. Infection is supposed to be more frequently due to crushed *Phlebotomes argentipes* than to bites. This could explain the fact that in India dogs are not subject to spontaneous infection. The disease in dogs is easily diagnosed by the cutaneous lesions, especially around the eyes and ears: seborrhea, alopecia, hardenings, nodules, and ulcerations.

4. MALARIA*

Malaria is probably the most widespread and least treated disease on the surface of the earth. In India it is estimated that there are 100 million cases of which only one-tenth are treated and these but casually. The countries of Africa, Asia, and Tropical America are affected throughout and, e.g., in the lower Congo, probably not a single native is exempt from malaria. Even in Europe (Balkans) and the United States there is a serious endemia. The disease is considered as the main obstacle to successful settlement in the warm countries. The part it plays in general world mortality is hard to judge, but is, without doubt, of the greatest importance.

Definition: Chronic infection caused by four species of Plasmodium, transmitted by the bite of various Anopheles: *Pl. vivax, malaria, falciparum,* and *ovale.* The disease is clinically characterized by fever, sometimes intermittent, anemia, and splenomegaly, and therapeutically by its response to quinine.

HISTORY

Intermittent fever had already been mentioned in Hippocratic writings. The modern story of malaria starts in 1638 with the introduction into Europe of the Peruvian bark of Cinchona. The story of the cure of Countess del Cinchon by this bark is considered apocryphal. The drug soon had a great success in Europe and facilitated the works of Morton (1666) and of Torti (Modène, 1658–1741) on the "fevers." The isolation of quinine dates from 1820 (Pelletier and Caventou) and has doubtless played a considerable historical part in the expansion of the white race. In 1847 Meckel drew attention to the presence of black pigments in the organs, and Kelsch found the same in the blood. The contemporary history dates from 1880. Laveran discovered the parasite in Constantine in the blood of patients suffering from malaria. Golgi, in 1885, described the asexual endoerythrocytic cycle (Golgi's cycle). In India, in 1897, Ross discovered the sexual cycle in the mosquito, and Grassi Bignami and Bastianelli in Italy (1898–1899) individualized the three human species and demonstrated their transmission by Anopheles.

In 1900 Manson succeeded in the definite transmission of malaria in London with mosquitoes infected in the Roman Campagna. The introduction of malaria therapy (Wagner v. Jauregg, 1917) has induced many repetitions of this experiment. The knowledge of exoerythrocytic forms (Raffaele, James and Tate, etc.) is quite recent and has been extended to human parasites after having been seen in birds.

Malaria has played an important part in history, particularly in wars and expeditions in the Balkans (First World War) and Near and Far East (Second World War).

GEOGRAPHIC DISTRIBUTION

The limits of endemicity are 60° N. and 40° S. but the affection predominates in low latitudes and with the gravest forms due to *Pl. falciparum.* Following a meridian in Europe and in Asia from Pole to Equator the following facts can be observed:

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* Paludisme is the correct French term. Malaria has the merit of having become international (in Italian it means "bad air").

1. Temperate zones (Western Europe for instance). Malaria of mediocre importance, due almost exclusively to *Pl. vivax.*

2. Regions with very hot summers (Southern Italy, Balkans). Mild springtime epidemic due to *Pl. vivax* in which relapses of the preceding year and cases of prolonged incubation play a large part. Estivo-autumnal wave of malignant malaria due to *Pl. falciparum.*

3. Tropical and equatorial regions (West and Central Africa). Hyperendemic zones where the seasons have less influence on the life of mosquitoes: predominance of *Pl. falciparum* with a state of premunition among the adult natives. Malaria is particularly important here.

Europe: Malaria disappeared from Belgium about 1870, in spite of the transmitting mosquito, *A. maculipennis atroparvus,* still remaining present. In Holland, in regions where there is brackish water, malaria still exists, but only in the form of mild tertian (*Pl. vivax*). The same parasite is to be found in Germany, North Russia, Hungary, Northern Italy, and isolated regions in France. Malaria is quite exceptional in England. In the Balkans and in South and Central Italy one finds at the same time *Pl. vivax* and *Pl. falciparum* and less frequently *Pl. malariae.* The endemicity is severe in certain regions: Balkans, Sardinia, and Corsica. Spain has very few cases.

Africa: With the exception of the Cape Colony, malaria exists everywhere.

Asia: Pl. vivax is widespread in the temperate part of Asia (North China) and *Pl. falciparum* in the hot regions.

America: Pl. falciparum plays an important role from the Southern U.S.A. to Central Argentina.

Oceanea: The only parts that escape are South Australia,* Tasmania and New Zealand, New Caledonia and also Micronesia and the small islands situated beyond the 170° meridian (absence of Anopheles).

ALTIMETRIC LIMIT

Malaria generally disappears at about 2,000 meters elevation, because of the lowering of the temperature. Yet cases have been quoted as contracted in the Andes at 3,000 meters and in Kenya at about 2,500 meters (see prophylaxis).

ETIOLOGY

Plasmodiums (Protozoa, order *Haemosporida,* family *Plasmodidae*) are characterized by an asexual and a sexual cycle. Man harbors the first of the cycles, called endogenous. The infecting forms, sporozoites, inoculated into his blood by the bite of an infected mosquito, penetrate the erythrocytes, develop there (trophozoites), and become mature forms, schizonts, ready for asexual reproduction or schizogony. These parasites stained by the Romanowsky method are composed of a mass of blue cytoplasm, rounded or amoeboid, and of a small, dense, red nucleus. The cytoplasm shows one or several vacuoles and contains also some pigment (hemozoine) produced by the decomposition of the hemoglobine by the parasite. It is estimated, however, that the sporozoites, after their introduction into the organism, first of all infect the cells of the histocytic system. These

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* A small focus, probably due to the war (repatriated soldiers), has been discovered in Brisbane. *A. annulipes,* proved vector, is found as far as Tasmania. The recent war has been responsible for similar new minor foci.

"cryptozoites," parasites without pigment in reticulo-endothelial cells, have been brought forward in avian plasmodiums. Up to the present, they have not been very clearly described in the plasmodiums of monkey and of man. Nevertheless, the latent phase, which lasts about a week between the infection of man and the infectious state of his blood, is actually interpreted not as the time required for the parasites to have attained a sufficient number, but more likely as a manifestation of an exoerythrocytic cycle.

Whatever the case may be, the parasites penetrate after a certain interval of time into the erythrocytes and prepare themselves, from then on to the schizogony. At this stage, the erythrocyte bursts. The "merozoites," freed in the plasma, penetrate the erythrocytes and begin anew the asexual cycle. The liberation of the merozoites in the plasma acts like an injection of foreign proteins and provokes the fever. The time which separates two schizogonies being constant for a given species (for instance, 48 to 72 hours), the interval between the attacks of fever is also regular (tertian or quartan). With multiple inoculations, every strain develops separately and attacks may be irregular and daily (quotidian). After a variable time of repeated schizogonies, certain parasites differentiate in sexual forms which attain their full development after a few days. The

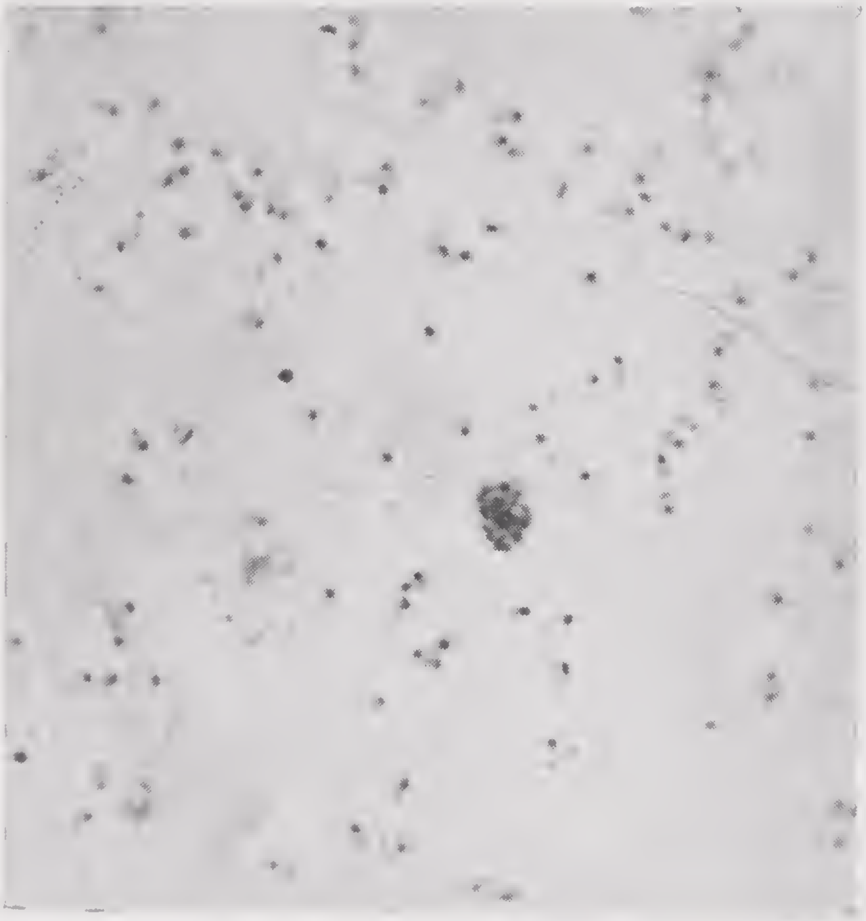

FIG. 19. STAINING OF PL. FALCIPARUM

Giemsa staining of a thick film in a heavy infection with *Pl. falciparum:* numerous small "rings" or schizonts and presence of a schizogony form, unusual for *Pl. falciparum* in the peripheric blood, except in very severe infections (coll. Tropical Institute, Antwerp) female macrogametocytes and male microgametocytes are the infective forms for the transmitting mosquitos and they will undergo in them the sexual cycle. The three species of *Plasmodium* common to man, *falciparum, vivax,* and *malariae,* have been known since the work of Grassi, Bastianelli, and Bignami (1898–1899). A fourth and much rarer species, *Pl. ovale,* was described in 1922 by Stephens. As a trophozoite or as a young schizont it is impossible to distinguish the different species in human blood. At an advanced stage, by the method of the thick film, the differentiation is generally possible. It is easy on thin smears of blood taken a few hours after the onset of a fever attack.

The following are the morphologic characters of the four species found in man:

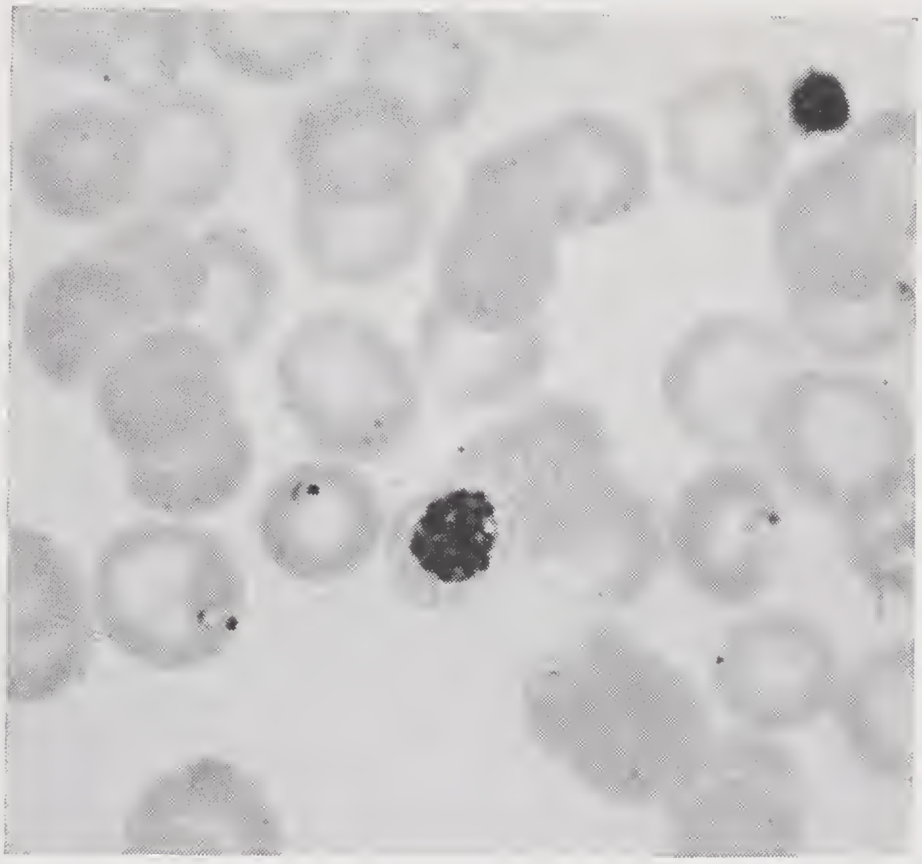

FIG. 20. THIN SMEAR OF THE SAME CASE AS FIG. 19

Plasmodium falciparum (48 hours' cycle): The schizonts usually have a ring shape, composed of cytoplasm surrounding a central vacuole and of one and sometimes two nuclear dots at the periphery. Two schizonts in the same erythrocyte are often found. Three and up to eight parasites may invade the red cells in massive infestations, the young schizonts then often having the shape of a rod without vacuole; a certain number among these are seen at the periphery or on the surface of the erythrocytes. The schizogony with an average of 16 merozoites generally does not occur in the peripheral blood (except in very massive and severe infections), but in the internal organs. In intensely colored blood smears little red brown spots, called the "Maurer spots," are sometimes seen in infected erythrocytes. They are considered by some as fragments of cytoplasm of the parasite abandoned by the retraction of the pseudopodes during sudden fixation of the smear. The gametocytes have a very characteristic shape of a half moon or of a banana, deforming the erythrocyte host, which is often hardly visible by a thin line in the concavity of the parasite.

Plasmodium vivax (48 hours' cycle): Young schizonts or "rings" are rare. The characteristic shape is polymorphic and amoeboid and contains several vacuoles. The erythrocyte host is full of refractile grains, yellowish brown (Schüffner's grains), the nature of which is not known. The schizogony of 16–20 merozoites occurs normally in peripheral blood. The fully developed gametocytes are rounded or oval-shaped. They do not contain vacuoles and often completely fill the erythrocyte. The microgametocytes have a rather dispersed nucleus, while the macrogametocytes have a nucleus which is more condensed in surface and in color, and grains of pigment which are thicker and more agglomerated. The parasites of *Pl. vivax* are generally met within macrocytes. On the other hand, it is known that reticulocytes are more susceptible to the infection by *Pl. vivax* than the older erythrocytes. The same does not apply to *Pl. falciparum* and *malariae*. Rather than as a result of parasitism, the large size of the infected erythrocytes is supposed to be due here to their youth.

Plasmodium malariae (72 hours' cycle): The parasitized erythrocytes are generally of small size. The schizonts often have a square or rod shape, crossing the whole diameter of the erythrocytes. In these, neither spots nor grains are found. "Rosaces" having an average of only 8 merozoites (6 to 12) are easily recognized in the peripheral blood and in thick drops. The gametocytes are smaller than those of *Pl. vivax*, but otherwise show the same characteristics.

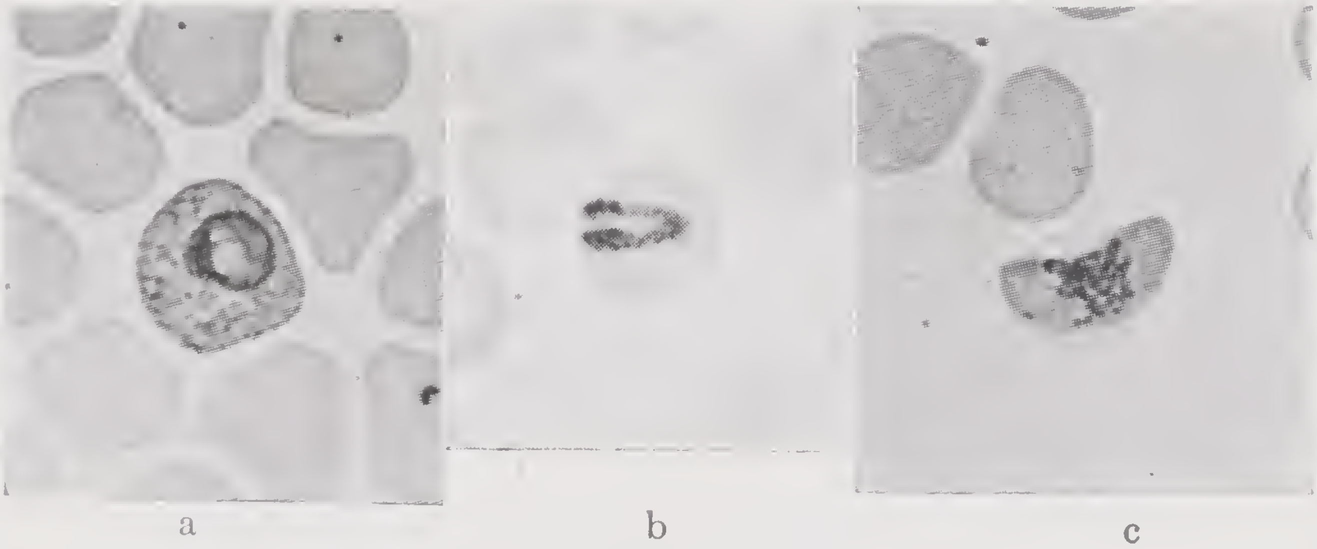

Fig. 21.
a. Schizont of *Pl. vivax* with Schüffner's dots
b. Schizont of *Pl. malariae*
c. Gametocyte of *Pl. falciparum*

Plasmodium ovale (48 hour's cycle): The morphology of this plasmodium is very close to that of *Pl. vivax*. The infected erythrocytes here are not only very large, but generally oval, and the grains of Schüffner appear early and are rather thick.

The *Plasmodiums of monkeys* are particularly interesting in so far as they are very similar to those of man. The African Anthropoides harbor three plasmodiums (*Pl. reichenowi, schwetzi,* and *rodhaini*) morphologically identical to, respectively, *Pl. falciparum, vivax,* and *malariae*. Cases of crossed susceptibility between chimpanzee and man (Rodhain) indicate the separation of the first two species, while the third seems identical in the two hosts. *Plasmodium pitheci* of the Borneo Orang Outang resembles *Pl. vivax*. The virus reservoir in Anthropoids seems to be only of theoretic importance. *Pl. knowlesi* of the *Macacus irus* of Borneo is easily transmitted to man

Plasmodium in birds (*Pl. praecox, Pl. gallinaceum*) have furnished important material for the study of the cycle and in therapeutic trials. Culture in vitro of plasmodiums has been obtained, but up to the present has shown little practical importance.

TRANSMISSION

Human plasmodiums are transmitted by Anopheles (*Culicidae*) mosquitoes which are recognizable by the fact that, placed on a wall, the line of the body generally slopes forward obliquely at 45° and is not parallel as with other mosquitoes. Their wings are generally spotted and palpae of the females are as long as the proboscis. The males, which are to be recognized by their plumous antennae, do not live on blood and are consequently not transmitters of malaria. The species determination is done on eggs, larvae, pupae, and adults. Examination of the eggs is often indispensable in order to determine the different varieties within the species. After one or two blood meals, the female Anopheles lays her eggs, separate and provided with lateral floaters, on the surface of water or in damp places. After one or three days, larvae are hatched which in ten to fifteen days, after four moulds, are transformed into pupae. These, after two or three days (sometimes very much longer), give birth to the imago or winged insect. A total of from ten to twenty days is required in favorable weather to ensure the metamorphosis.

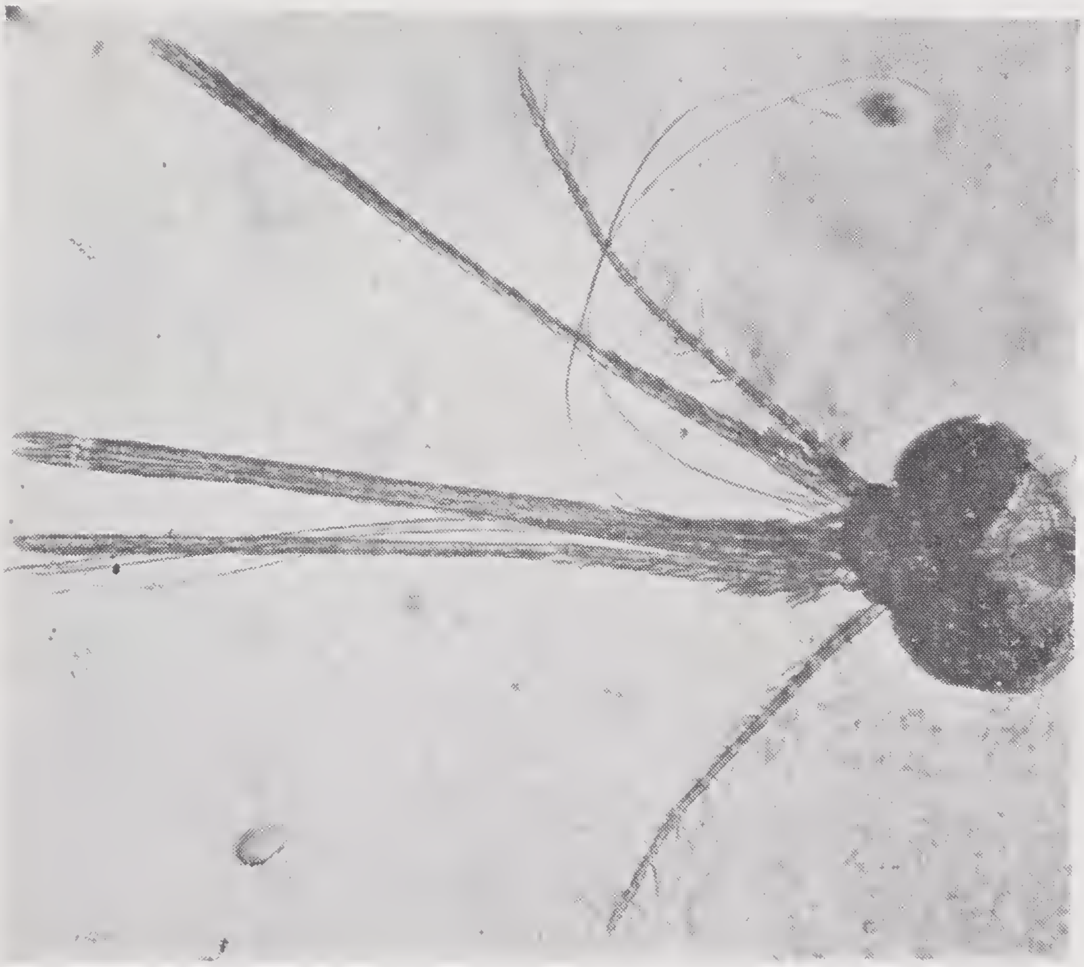

Fig. 22. Buccal Pieces of Anopheles sp.
Phot. R. Resseler, Tropical Institute, Antwerp

About sixty species of Anopheles (among nearly two hundred known species) have been recognized as transmitters of human plasmodiums (experimental or natural infections). Only a few have yet proved to be important vectors: especially those who bite man (anthropophilic) more frequently than animals (zoophilic), and more inside houses (endophilic) than outside (exophilic). But the capacity of transmitting malaria depends on innumerable factors, the study of which is far from completed. Precise observations of the ethology (seasonal variations, flight range, nature of breeding places, length of life, biting habits, etc.) of the different species of Anopheles, those of the numerous varieties within each species (some acting as vectors and others not), those also of every species or variety in different regions (vectors limited in geographic distribution) as well as precise biochemical research will help to throw much light on facts which are still obscure.

The following is a list of the most important Anopheles known as vectors of human malaria.

Europe	*A. maculipennis* (different biotypes in different regions)
North America	*A. quadrimaculatus*
	A. maculipennis var. freeborni
Central and South America	*A. albimanus* (Caribbean archipelago)
	A. bellator (Trinidad)
	A. darlingi (Guyane, Brazil, Venezuela)
	A. gambiae (introduced in 1930 in Brazil)
	A. pseudopunctipennis (Mexico and Central America, Andes region from Colombia to Argentina)
Africa	*A. multicolor* (North Africa)
	A. funestus
	A. gambiae
	A. moucheti
	A. pharoensis
	A. nili
India	*A. culicifacies* (Ceylon)
	A. stephensi (Bombay)
Far East	*A. culicifacies* (Burma)
	A. hyrcanus sinensis (China, Japan)
	A. maculatus (Malaya and Java)
	A. minimus (Philippines)
	A. subpictus (Java)
	A. sundaicus (Sumatra)
Australia and Pacific Islands	*A. bancrofti*
	A. punctulatus

The geographic distribution indicated within parentheses are those where the quoted Anopheles plays a particularly important part. This varies from one region to another. For instance: *A. pseudopunctipennis* is a much more important vector in North Argentina than in Mexico, and while *A. maculatus* is the most feared in Malaya, *A. minimus* is a much more important vector in the Philippines. A change in local conditions can also favor the development of a less important species and render it very dangerous (epidemic in Sumatra transmitted by *A. hyrcanus* as the result of extension of ricefields after the war).

Malaria can spread only through Anopheles vectors (definite hosts) infected on human beings who carry ripe gametocytes in their circulating blood (intermediate hosts). It has been determined that the Anopheles become infected only under certain conditions. First of all, a certain number of gametocytes, varying according to the Anopheles, is necessary per cc. of human blood. The proportion of male and female gametocytes and their age are equally important. One even wonders if the greater part of the Anopheles are not potential vectors of malaria. As a matter of fact, observations and experiences which have forced many writers to exclude the part played by certain Anopheles did not take the above mentioned particularities into account and did not draw attention to the number of gametocytes present in infecting blood.

The gametocytes of Plasmodium attain full maturity only in the stomach of the Anopheles mosquito (artificially also in vitro in the blood, as first observed by Laveran). The microgametocyte becomes round and on its surface six microgametes of long and flagellated shape originate (exflagellation). The microgametes free themselves and one of them fertilizes a macrogametocyte which has also reached maturity and transformed into a spherical macrogamete. The latter changes into a zygote called ookinete, because it is immediately provided with independent movements. The ookinete moves about in between cells of the stomach of the mosquito until it stops under the coelomic membrane of this organ. The nucleus then divides rapidly and the cytoplasm splits inside the membrane of the ookinete. The latter grows and becomes a sporocyst crammed with sporozoites and spurting out on the surface of the stomach. The sporocysts burst and liberate the sporozoites in the coelomic cavity The sporozoites, long and extremely mobile, accumulate electively in the salivary glands of the Anopheles from where they are injected during the bite by the thin venemo-salivary duct of the hypopharynx. The duration of the cycle in the Anopheles varies greatly according to the temperature and the degree of humidity in the air. In optimal conditions (from 20 to 27 C. and from 50 to 75 per cent humidity) the cycle is accomplished in eight to ten days. The length of the cycle varies for the three species of human malaria: at 20 C. it is shortest for *vivax* and longest for *malariae*. There also exist specific differences in the disposition of spots of pigment on young oocysts and in the size of sporocysts.

Congenital transmission through the placenta may occur. This has been observed in cases where the transmission by Anopheles could be excluded, for instance in Europe during the winter, and especially with *Pl. vivax*. In the endemic area, however, among natives who acquire premunition in adulthood, congenital transmission seems very rare in spite of the abundance of *Pl. falciparum* in the placenta. (Blacklock and Gordon in Sierra Leone, Van den Branden and Henry at Leopoldville, Clark in Panama, Garhnam in Kenya.)

Pathology: This will be studied, further, together with the clinical manifestations observed in the various organs.

PATHOGENESIS

As Golgi established in 1885, for *Pl. malariae,* the fever attack is combined with the liberation of the merozoites. The merozoites and the substances liberated during the schizogony can be considered as toxins, in a broad sense, or at least as foreign proteins of which the pyretogene role played in case of direct introduction into the blood is well known. Abrami and other French writers mention a hemoclastic crisis with shivering, arterial hypotension, leukopenia and a general anaphylactic picture.

Anemia is first of all direct: the parasites multiply (fortunately immunity rapidly decreases the reason for this theoretically geometric progression) and every parasitised erythrocyte is destroyed by the schizogony. An indirect "toxic" anemia may perhaps develop in addition to direct anemia. A third pathogenous mechanism is due to the obstruction of capillaries realized by *Pl. falciparum,* producing, therefore, pernicious attacks (see further).

SYMPTOMATOLOGY

The incubation is variable and often estimated as follows: 9–14 days for *Pl. falciparum;* 11–21 days for *Pl. vivax;* 27–32 days for *Pl. malariae.*

In Holland and Finland, *Pl. vivax* frequently has an incubation period of from seven to nine months, the attacks making their appearance about June, while the infection takes place in October. The nature of the strain of malaria is probably responsible here. Yet by injection there is no prolonged latency. The ordinary period of incubation includes the period required for the exoerythrocytic development, then the necessary time for the trophozoites to multiply to the extent of attaining the pyrogenic limit. It does not seem necessary to consider a sensitization of the organism as for other infectious diseases, as the incubation may be reduced to the minimum in cases of massive inoculation by syringe (three days). While the exoerythrocytic stage of the cycle lasts, the circulating blood is not infectious, even given in large amounts.

The pyrogenic limit is difficult to determine as it depends on the state of immunity of the subject. With new subjects it is estimated that 200 to 300 *Pl. vivax* or *malariae* per cu. mm. are sufficient to cause fever. The limit for *Pl. falciparum* would be 600–1000 per cu. mm.

INVASION

Classic signs such as a sharp onset and intermittent fever are not constant. This picture is often seen with *Pl. malariae,* less frequently with *Pl. vivax,* and even less with *Pl. falciparum.* With these last, one often observes a progressive start followed by a subcontinuous or remittent fever with slight initial shivering. This is the malaria type called "primary" by French and Italian writers. It is also seen in therapeutic malaria and was called "acclimatization fever" by the older colonials. As such it may possibly be a serious type of malaria, at any rate when due to *Pl. falciparum* which might give a pernicious infection. There is a less favorable response to treatment. The parasites are not always numerous in the peripheral blood and the clinical diagnosis often mistakes it for influenza, typhoid fever, or meningitis. Subjects who make use of chemical prophylaxis often escape this first invasion and later show sharp attacks. This is also the case with late relapses. Primary malaria is possible only in subjects who are new for the parasite species. Even other strains of the same species will not result in the reappearance of this clinical aspect, but simply of typical attacks.

General symptomatology of malaria might be divided into (A) paroxysmal symptoms (rather improperly named acute malaria), and (B) chronic symptoms of blood and visceral alterations.

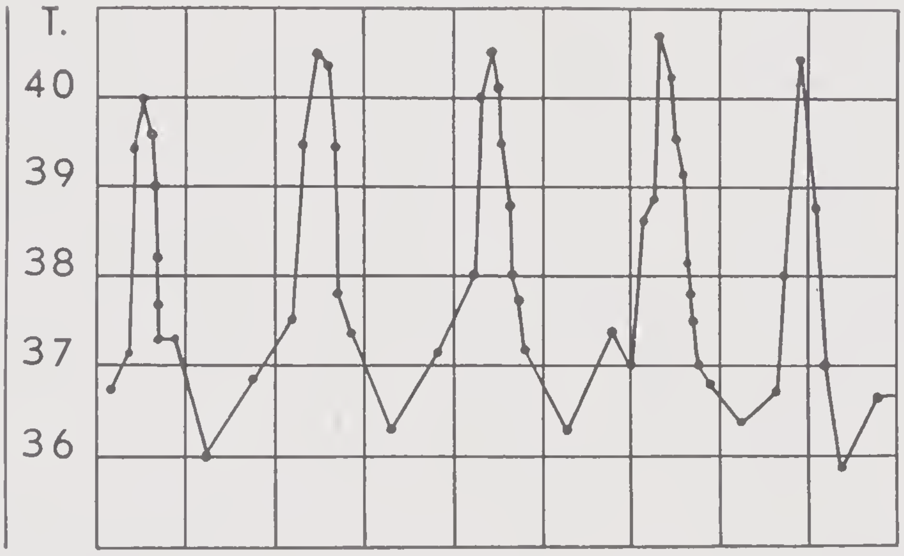

Chart 5. Benign tertian in malaria therapy (Dr. Rodhain)

(*A*) *Paroxysmal Symptoms*

These are essentially fever and the discomfort resulting from it. In the most typical cases, mostly due to the large parasites (*Pl. vivax* and *malariae*), the fever is characterized by intermittent and periodic attacks, appearing diurnally (10–16 hours) and lasting six to twenty-four hours. These attacks have very marked phases: (1) shivering, cyanosis ($^1/_2$–2 hours); (2) heat (5–10 hours) with dry skin, facial congestion; (3) intense sudation (1–3 hours).

The associated discomforts are commonplace: headache, alimentary or toxic vomiting, psychonervous excitement or depression. The circulation shows tachycardia, increase of arterial pressure when the attacks start, passing systolic murmurs. The splenic region may be painful.

Regarding periodicity, one distinguishes (1) quotidian fever, twenty-four hours between each attack; (2) tertian fever, forty-eight hours between each attack; (3) quartan fever, seventy-two hours between each attack. The interval of forty-eight hours corresponds with the schizogonic development of *Pl. ovale*, *vivax* and *falciparum*, that of 72 hours with *Pl. malariae*.

The daily periodicity is attributed either to multiple infections (double tertian, triple quartan) or to mixed ones (two or three species of parasites), with a sufficient interval between generations.

After the period of incubation there are often irregular generations of parasites, but by degrees only one or two principal generations continue to subsist with the corresponding attacks. The reverse may also occur: the splitting of a single generation and a tertian, for instance, becoming daily. During the apyretic intervals the general state of health may be practically normal (in benign tertian); at other times great depression persists, etc.

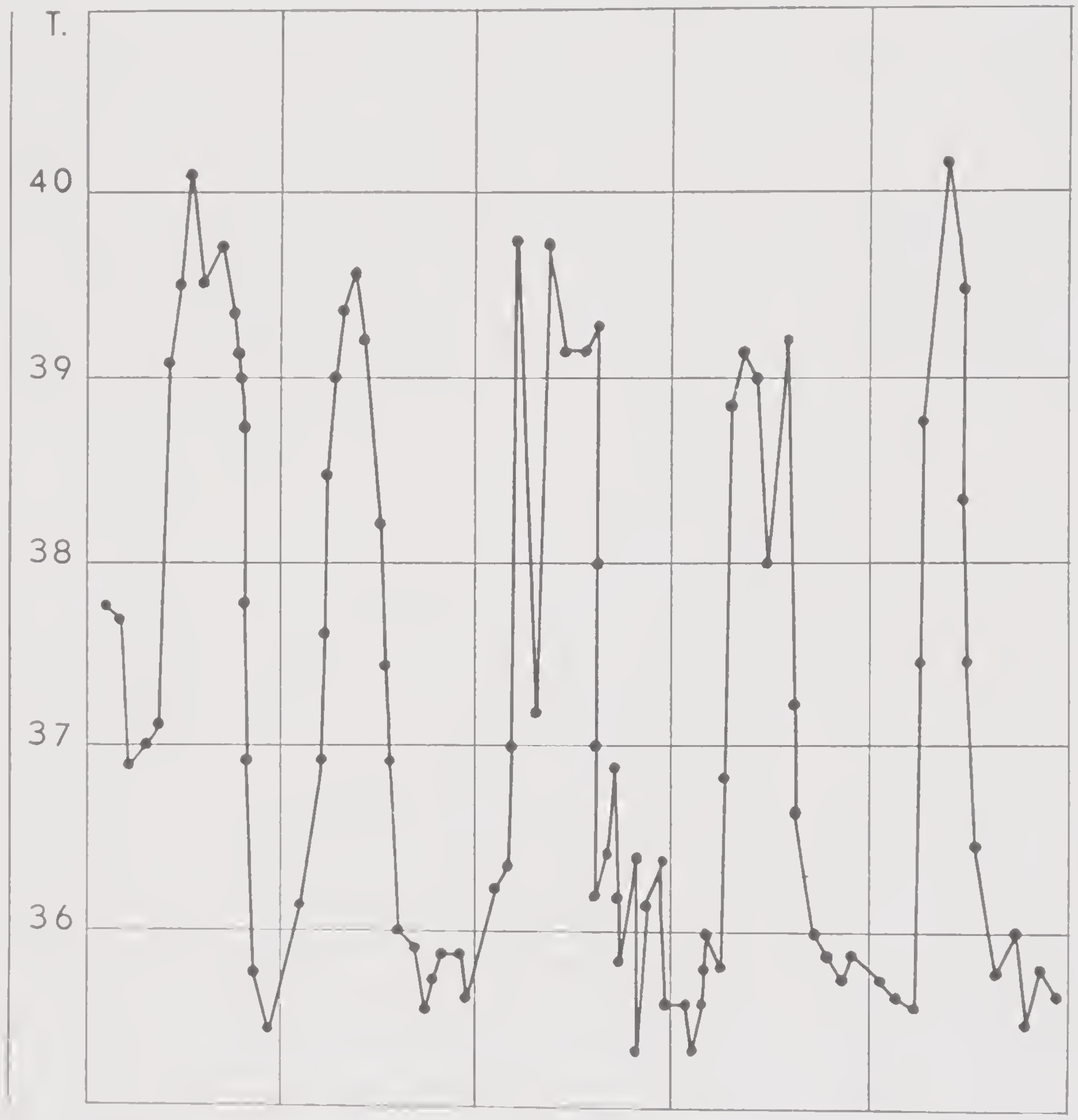

CHART 6. Daily fever. Case of malaria therapy with *Pl. vivax* (Dr. Rodhain)

BENIGN TERTIAN FEVER

In experimental inoculations by mosquitoes one often observes two to five days of subcontinuous fever; then attacks become quotidian. During this period the attacks are very clearly defined, in "tower" form, the temperature is high but the general state of health is ordinarily good and the evolution fairly mild. Herpes labialis is frequent. Attacks are sometimes repeated 10–20–30 times during the months following the onset. After that there are fewer relapses for several months, before again becoming more frequent about the eighth or tenth month after infection.

A spontaneous cure is sometimes observed after a year and is more generally seen two or three years afterwards. If the subject is treated, relapses are very irregular, but are met in most cases.

Pl. ovale infection: It produces fairly similar attacks. According to Mühlens they show a tendency to appear toward night.

QUARTAN FEVER

It often starts with isolated attacks which sometimes go on for a considerable length of time. They have the "tower" form. Shivering is very intense and prolonged, the temperature very high. Nephritis may complicate the generally rather mild evolution.

TROPICAL FEVER

Pl. falciparum frequently produces at the onset a fever of the continuous or subcontinuous type, "primary malaria" of French observers, "acclimatization fever" of old colonials. Subsequently the attacks sometimes show less clearly defined phases than those caused by other parasites: feeble shivering, slight sudation. They have a more pronounced evolution, in "plateau," with sometimes a pseudocrisis, and they can spread out in twenty or twenty-four hours. It is conceivable, if the temperature is not taken frequently (every four hours), that a short remission might escape unnoticed, and that one could be inclined to exaggerate the continuous character of the fever curve. The toxi-infectious phenomena are often marked and life is directly threatened. If the disease is allowed to develop,

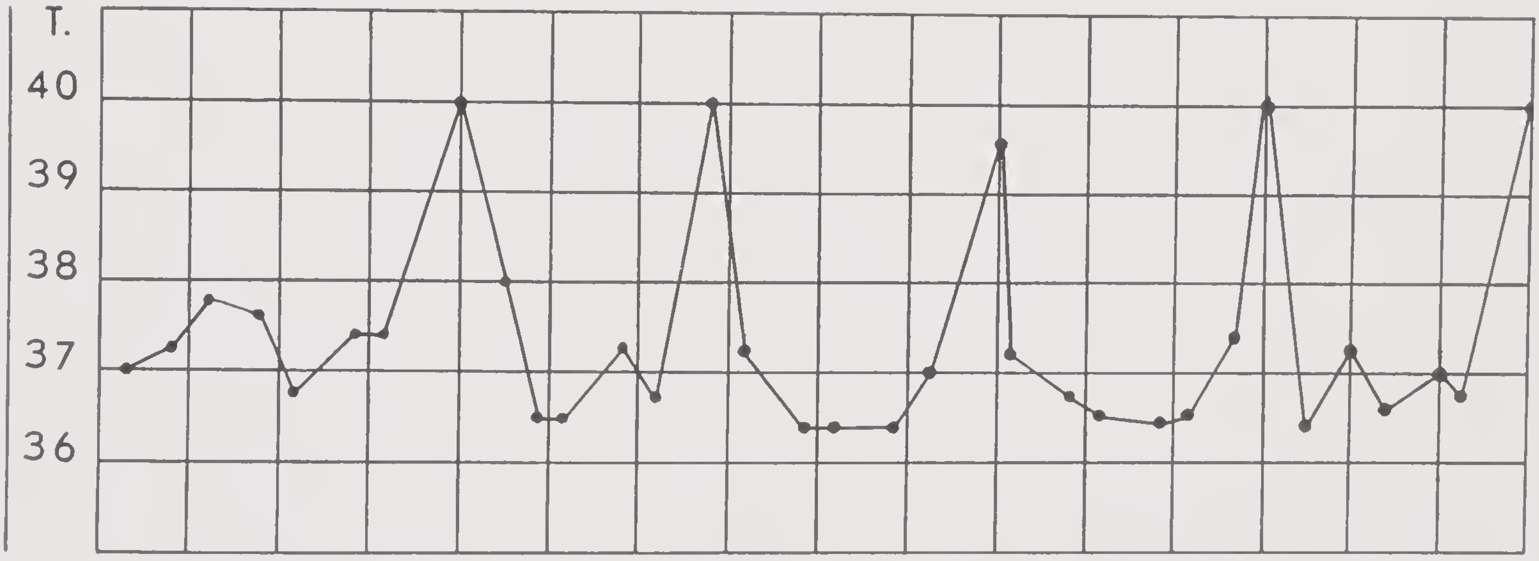

Chart 7. *Pl. malariae* with quartian fever (Dr. Rodhain)

a dangerous procedure which has, however, been done experimentally, the first attack will be followed in the next months by febrile recrudescences of eight to ten days separated by apyretic intervals of five to fifteen days. This condition will hasten the patient's death or he may recover fairly quickly (six months).

Pernicious forms of malaria are mostly due to *Pl. falciparum*. This species shows little tendency to relapses at long intervals.

Clinical Varieties of Acute Malaria

BENIGN MALARIA

Attention should be drawn to this form which is often met in our present colonials, following chemical and mechanical prophylaxis. The attacks are typical but mild, short, and often disappearing without repetition after the first day of treatment (even with *Pl. falciparum*). It is possible that these subjects have acquired a certain degree of immunity through chemical prophylaxis.

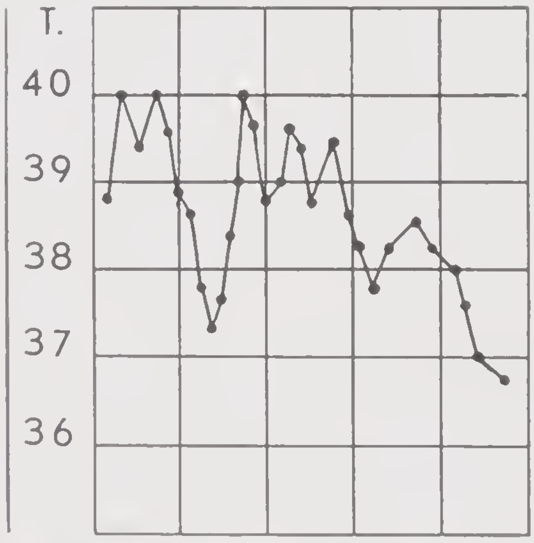

Chart 8. Malign tertian. Same case as in No. 1, one month previously. Double infection with *Pl. falciparum* and *Tr. gambiense* (Dr. Broden)

LATENT MALARIA

This means without any clinical phenomena. The form is often latent in Africa and appears in Europe after cessation of chemical prophylaxis. This is an exaggeration of the general appearance of the sickness, the relapses of which are separated by long, healthy periods. Whether the parasites responsible for the relapse are to be found in the viscera (spleen, etc.) or in small numbers in the circulating blood, has not been clearly established. In support of the second hypothesis we have the common incidence of accidental transmission of the infection after transfusions of blood by donors who have chronic or latent malaria. The production of "provoked" attacks will be dealt with further.

MASKED MALARIA

Local symptoms (neuralgias, etc.) or general ones (anemia, digestive malaise, etc.) are here observed. They are attributed, more or less positively, to the malarial infection (antecedents, response to quinine, paroxysmal evolution).

The local symptoms are of a rather dubious origin. Even the action of quinine should be interpreted with care. The general symptoms are those of a chronic evolution without much fever and they may lead to very severe accidents (hemoglobinuria). Parasites are sometimes found in the blood of Europeans who complain of no fever.

Next to these minor forms, febrile malaria also presents very severe clinical types. Their exceptional gravity is due sometimes to the intensity of the infection, the patient dying in a few days' time from toxi-infection and exhaustion (perniciosita subcontinua of Marchiafava). Other severe forms are related to visceral localizations due to the fact that the schizogony of *Pl. falciparum* occurs in the capillaries of the internal organs. Vascular, and consequently visceral, troubles result from this pathologic condition and are responsible for the pernicious (sensu stricto) attacks (perniciosita comitata of Marchiafava).

Pl. falciparum is especially responsible for these two severe forms of malaria. Recently, however, lethal cerebral forms have been observed with *Pl. vivax* in Russia.

SEVERE FORMS (WITH MASSIVE SEPTICEMIA)

(a) *Remittent bilious fever* of French authors ("subcontinua biliosa o itterica" of the Italians). The name indicates the symptomatology sufficiently. The prognosis is severe if energetic treatment does not intervene (adynamia).

(b) *Continuous malaria* ("subcontinua typhoide" of the Italian authors; primary malaria of the French; acclimatization fever). It is mostly seen at the beginning of infections, especially with *Pl. falciparum,* in heavily exposed individuals. Here too, adynamia or coma threatens the patient.

PERNICIOUS FORMS

These are seen relatively early in the infection (practically always *Pl. falciparum* cases), when immunity is still weak. Marchiafava observed that such cases rarely showed the classic enlarged spleen. Bastianelli nearly always noticed perniciocity during the course of primary malaria. Its mechanism is double. First of all, the virulence of *Pl. falciparum* itself produces in certain weak subjects a very intense infection. The possibility of perniciocity becomes a definite danger as soon as the number of parasitised globules reaches 6 per cent. The presence of division forms of *Pl. falciparum* in peripheral blood implies a severe prognosis. Secondly comes the fact of the frequency in this infection of clumps of parasitised erythrocytes adhering to the inner wall of the capillaries and causing local toxic or circulatory lesions, which have been particularly noted in the brain: obstruction and slight hemorrhage of the capillaries, alteration of the neurones, proliferation of neuroglia, cellular infiltration producing small gliomesenchymatous nodules (Dürck's malarial granuloma), to be found especially in the white matter. It is quite possible that during the cerebral attacks a congestive and microhemorrhagic aspect may be noted which resembles the encephalitic appearance of different infections. Certain French writers have observed a marked hyperazotemia in the course of cerebral attacks.

Clinical Types of Pernicious Attacks: The most frequent is the comatose cerebral attack, sometimes hyperpyretic, or, on the contrary, with a relatively low temperature. At the start the appearance is that of a common malaria attack, but torpor develops rapidly and increases until it reaches a state of coma. Circulatory adynamia sets in and the patient may die in a few hours or in one or two days. The prognosis of this form is severe. The differential diagnosis is difficult with infectious febrile comas (antecedents, characteristics) and with heat stroke. Happily, blood examination provides definite diagnosis in most cases. However, fatal cases have been reported, where cerebral capillaries only contained parasites (Kahn, 1945).

Attacks with Delirium: sometimes accompanied by aggressiveness. The "Amok," met with among Malayans, is fairly often a psychic reaction to malaria, but may as well be devoid of infectious basis.

Attacks with Convulsions: meningitic or eclamptic fits mainly observed among children.

Pernicious Algid Forms: usually with low skin temperature, and tendency to collapse (shock). The symptoms observed in these cases are attributed to the localization of the parasites in various viscera, particularly abdominal ones. Clinically, they may resemble cholera (diarrhea with dehydration and collapse), dysentery (blood-stained stools), or several abdominal conditions warranting surgery.

The parasites block the capillaries of the villi, as they do those of the brain. It has occasionally been possible to find the parasites in the blood of the stools. This dysenteric form seems to be more common than the choleriform one. Needless to say, the diagnosis must eliminate the possibility of cholera and bacillary or amebic dysentery superimposed on malaria.

Some rare forms must still be noted: hemorrhagic, anginal (simulating angor pectoris, and due, no doubt, to the localization of parasites in the vessels of the myocardium), and diaphoretic ones (with excessive sudation and collapse).

Pneumonias and broncho-pneumonia, determined by the localization of the parasites have been observed also. These diagnoses must, of course, be well ascertained: the coexistence of angina pectoris or pneumonia, with malaria as an independent disease, is possible. The human mind is only too prone to rely on appearances and fasten on the easy solution. However, such cases exist, especially, it seems, among seriously infected and overtired soldiers during both World Wars. A specific treatment must be devised in time and carried out with energy.

Seyfarth used to insist on the vascular character of this infection and to distinguish the following as causes of death, nearly always attributable to *Pl. falciparum:*

1. Septicemic forms. (30 per cent of deaths.)
2. Cerebral forms. (55 per cent. These forms correspond to the pernicious attacks with capillary and pericapillary lesions in the brain.)
3. Cardiac forms. (14 per cent. Algid forms with parasites acting as emboli in the coronary system.)
4. Renal forms. (1 per cent Nephritis.)

It will be noticed that blackwater fever is not included in this series.

(*B*) *Constant Symptoms and Lesions*

1. *The Blood. Red Corpuscles:* Anemia never fails to be present; the patient may lose more than a million R.B.C. per cu. mm. in the course of an attack. The anemia remains moderate in benign cases.

The anemia is of the normo- or hypochromic type, with signs of regeneration, particularly reticulocytosis. The alterations due to the parasites (Schüffner's, Maurer's dots)are characteristic of the infection.

Leukocytes: At the beginning of an attack, there is a polymorphonuclear leukocytosis with shift to the left. At the end of the attack, there is neutropenia and monocytosis. The latter is characteristic of the apyrexial intervals in chronic malaria, which should then be suspected. (Over 15 per cent monocytes.) Leukocytes loaded with pigment are rare but pathognomonic.

Plasma: Hyperbilirubinemia is about the only feature reported. The Bordet-Wassermann, Kahn reactions, etc., may be positive during an attack in nonsyphilitic patients. They are not positive in cases of latent or very chronic malaria (adult natives), or after treatment (negativation after three or four weeks).

Pigments: The black pigment or hemozoin* which results from the plasmodial attack on hemoglobin, is really hematin. This substance is practically insoluble, except in concentrated alkali or aqueous ammonium sulphide. It does not give the Prussian blue reaction, though iron is present in a concealed form. Hemozoin is seen in the blood monocytes, but even more in the fixed reticulo-endothelial cells, and particularly in those of the liver and especially of the spleen. This compound is probably similar to the black pigment which accumulates in the Küpffer cells in entero-hepatic forms of schistosomiasis. The repartition of this insoluble pigment is comparable to the phagocytosis of India ink injected intravenously. Hemosiderin, which is an ochre nonspecific pigment, is found during most hemolytic processes in various types of cells, including the

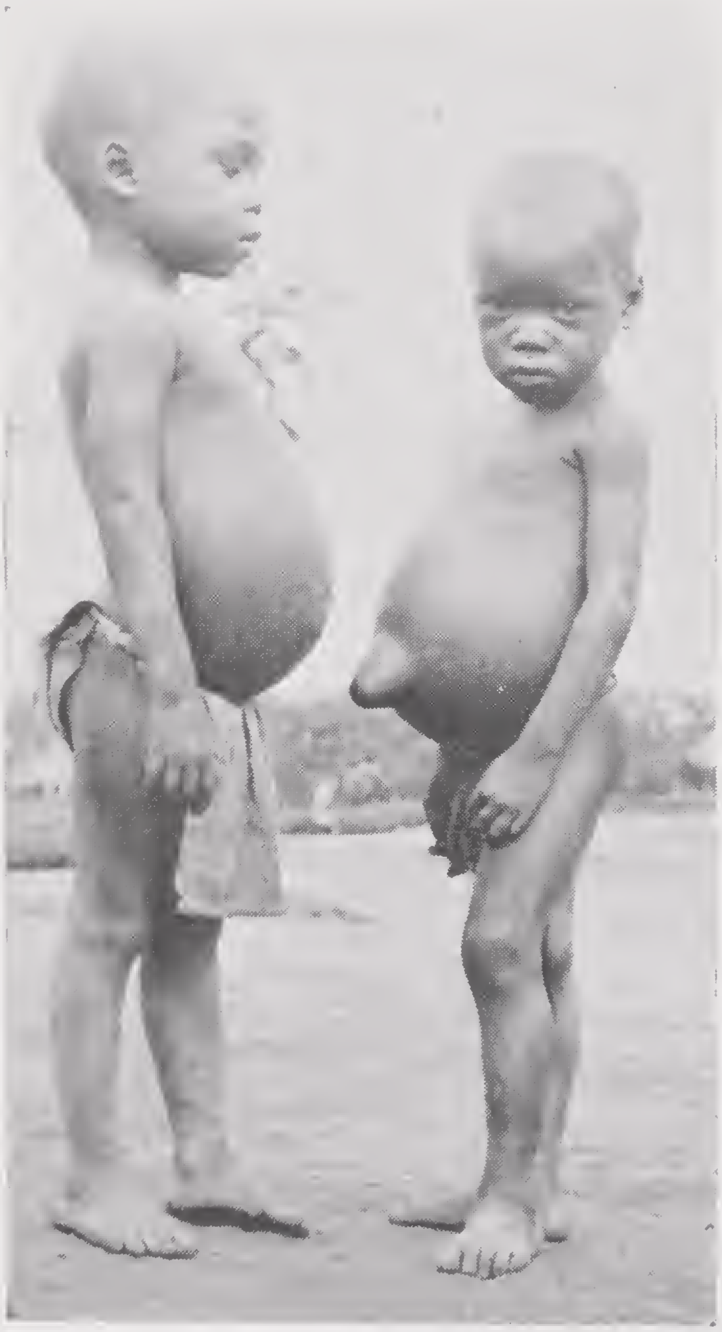

FIG. 23. "HEALTHY" CHILDREN WITH SPLENOMEGALY AND ABDOMINAL DILATATION, CONGO

Phot. L. van den Berghe

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* The word melanin must be used for cutaneous pigment only.

liver and kidney epithelium. It gives the Prussian blue reaction. The black pigment is responsible for the slaty grey coloration of various organs in chronic malaria (brain, spleen). The muddy complexion of the chronic case of malaria is due to a mixture of anemia and skin pigmentation.

2. *The Spleen:* From the first acute attack, it is congested, sometimes tender, and percussion may show transitory increase in size.

Among contemporary colonials, apart from unfavorable circumstances (war, etc.), therapeutic measures are usually efficacious, and plenomegaly does not develop to any great degree. It may be otherwise among white children whose paludism is neglected and who show splenic reactions more easily. The same thing happens among the "poor whites." Splenomegaly can be observed more clearly among native children, whose disease follows its course unmodified, or nearly unmodified by treatment. The splenic index is the easiest criterion of the degree of malaria in a region. It is, however, always inferior to the parasite index (obtained from the study of thick films). It must be pointed out that there are other causes of splenomegaly, but some are rather rare and others mainly affect adults. (Leukemias, Hodgkin's disease, schistosomiasis, etc.)

Schüffner uses the following classification: a line is drawn along the left costal arch, and a second line parallel to the first is traced from the umbilicus; these two lines are bisected by a third passing through the apex of the spleen. This third line is divided into 4 equal segments, thus giving the splenic sizes as 1, 2, 3, 4. The extension of this line from the level of the umbilicus to that of the pubis is also divided in 4, giving the sizes 5, 6, 7, 8. There is a spontaneous trend toward resolution of this splenomegaly. The index among native adults is much inferior to the rate among children.*

Clinically, it is not very important, though cases of traumatic or even spontaneous rupture of the spleen have been occasionally recorded, mainly with *Pl. vivax*. Displacement or deviation of the stomach and colon has also been observed. The spleen plays a considerable part in the defense against plasmodial infections. Fatal forms or forms showing great resistance to treatment have been seen after splenectomy, or in case of congenital absence of the spleen.

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* The index of Ross is often used with only four grades: Add the number of hypertrophied spleens of each category and multiply by the number of the category. Divide by the number of splenomegalic subjects. For example:

10 subjects I=40
20 " II=90
30 " III=40
10 " IV=10
180 : 70=2.57

The volume of the spleen increases until the immunity is well established, then decreases together with the number of parasites. At the beginning of the infection the parasites are scarce with a normal spleen.

Anatomically, the spleen presents a congested and soft appearance in acute attacks, as well as a blackish tinge more or less noticeable according to the amount of pigment and to the degree of congestion. In chronic cases, congestion disappears, but the organ becomes more solid and more voluminous from an increase of the endothelial tissue (it sometimes weighs several kilos in cases infected by *Pl. vivax*). Later, fibrosis and perisplenitis make their appearance. Histologically, in acute cases, the appearances are those of congestion, with numerous parasites, as well of the trophozoite as of the gametocyte type. Pigment is deposited in the macrophages of the red pulp and sinusoids. These macrophages also display intense phagocytic activity against parasitised cells. Ultimately, the pigment tends to appear no longer as small granules, but as larger blocks, which even become extracellular.

The Malpighian bodies shrink, but present young cells which replace the lymphocytes. Some authors accept as a fact that the latter become macrophages. After cure of the disease, the spleen returns to a more normal appearance (the follicles in particular), and the pigment finally disappears, in a way which is as yet not definitely determined.

3. *Liver:* There is often slight liver hypertrophy, which can resolve itself. During severe attacks, an icteric or subicteric tinge of the skin is not rare. Of a total of 3,000 cases observed in Hamburg over 25 years, 80 per cent of cases showed subicterus, and 1.5 per cent icterus (this symptom is a regular concomitant of bilious remittent fever).

Anatomically, the features are congestion and cellular hyperplasia of the Küpffer cells with phagocytosis of the pigment occurs. In chronic cases, the latter is localized in the portal spaces, instead of spreading over the lobule (acute cases). Parenchyma cells may show alterations, and in severe cases fatty degeneration and necrosis may develop, though not so markedly as in yellow fever. Parasites are moderately numerous. Hepatic cirrhosis of malarial origin is not well established either clinically or anatomically. It is well known that precirrhotic and cirrhotic processes are common among natives in the tropics.

4. *Gastrointestinal Tract:* Anorexia with hypochlorhydria is often observed among patients suffering from malaria. In endemic areas, digestive troubles and vomiting may be signs of malaria. Loading of the small vessels of the intestinal mucosa with *Pl. falciparum* may lead to local dysenteric symptoms (algid forms). Various lesions have been observed, but they may be due to complications.

5. *Bone Marrow:* Parasites may be numerous here. The marrow often

presents an erythroblastic appearance and pigment deposits. Aplastic phenomena might be observed in cachectic cases.

6. *Lungs:* The existence of real pneumopaludism is a little doubtful. Small local lesions due to "parasitic thrombosis" of capillaries have been observed, however.

7. *Heart:* The same pathogenic mechanism has been shown to be at work: packing of the vessels with parasites and myocarditis, fatty degeneration, small subendocardial hemorrhages, and flabby and dilated muscle wall. Clinically, cardiac dilatation and hypotension may be present. At the beginning of the attacks, at the shivering stage, the tension is raised.

8. *Suprarenals:* The accumulation of parasites in this organ and the resulting local disturbances have been given as explanation of adynamic attacks, and pituitary localization as an intervening cause in "malarial hypoglycemia."

9. *Kidneys:* Febrile albuminuria, though seen in tropical fevers, remains unimportant. Urobilinuria is the rule, and its absence is a good sign of cure. Some authors state that a hemoglobinuria, detectable only by chemical methods, often exists in tertian malaria. It would be interesting to verify this fact. Chloride elimination diminishes during an attack, but returns when it ceases. Renal lesions are uncommon, except, perhaps, in cases of quartan fever, where lipoid nephrosis with some alteration of the glomeruli may be observed.

10. *Brain:* We have already mentioned pernicious attacks, in particular cerebral ones. We also noted the considerable variety of its manifestations, the most common being somnolence or pyrexial malarial coma. Neck rigidity and mental confusion are also common. These accidents often have an abrupt onset and a rapid evolution; hence the importance of prompt diagnosis and treatment. Indeed, the mortality is appreciable. Fitz Heigh and colleagues in India report 140 cerebral cases over a total of 6,000 cases (i.e., 2.3 per cent). The mortality among these cerebral cases was 5 per cent in a group placed in favorable circumstances and 33 per cent in another. We have already stated that the intracapillary conglomeration of parasites (which is not confined to the brain, but more dangerous in its effects at that level) determines the cerebral manifestations which occur, possibly through the intermediary of local circulatory disturbances (pseudo-thrombosis by parasitised globules).

Macroscopically, the brain presents a slaty grey appearance in the grey matter, with normally colored white matter. Petechiae are found in the white matter, whether subcortical or other, and including the internal capsule and the cerebellum.

Microscopically, we see pericapillary hemorrhages, small hemorrhagic and necrotic malarial granulomata with glial cells around the foci (which must be differentiated from the foci of different forms of encephalitis by the presence of parasites or pigment).

Apart from acute pernicious attacks, a number of psychic and nervous disturbances, whose relation to malaria is ill established, have been described as sequelae of paludism. One must also remember the psychosis due to atabrin. This, together with an erroneous positive Bordet-Wassermann reaction, might induce the wrong diagnosis of general paralysis (Allen, 1944).

11. *Other Points:* One should interpret with prudence amblyopia, auditive troubles, exanthemata, etc. Herpetic keratitis, as well as herpes, might be more frequent among patients suffering from malaria. Lewy (1945) described a malarial papillitis.

12. *Placenta:* The placenta is always very rich in parasites (*Pl. falciparum*) owing to its slow circulation. Relapses are common among pregnant or recently delivered women. Transplacental transmission, on the contrary, is uncommon. It probably denotes the presence of local lesions. It is seen, above all, among subjects without premunition, and more especially in *Pl. vivax* infections. Abortion is a possible complication. Blacklock and Gordon believe that intense placental infection may be a cause of stillbirths (one should, however, consider the possibility of sickle cell anemia).

Chronic Malaria

Malaria is always chronic. However, we refer here to cases where pyrexia is not very noticeable, but where anemia, splenomegaly, digestive troubles, and disturbances of general health occur, and which produce a muddy complexion in white people.

This state culminates in "malarial cachexia," but other factors associated with cachexia must be eliminated, as they are often more potent: worms, kala-azar, famine, etc. We have here the picture of all great cachexias: anemia, wasting (general and muscular), edema, cardiac disturbances, and hemorrhage, more particularly of the retina, etc.

In young patients, infantilism due to malaria may be observed, at least in the white race.

Organic Sequelae: Most experts admit that malaria can be cured without leaving any noticeable sequelae. One must think twice before attributing to this etiology such conditions as hepatic cirrhosis, aortitis, nephritis, etc.

The Belgian scale of indemnity for disablement admits from 20 to 100 per cent disablement, subject to review within legally prescribed periods. The natives of the Congo, after fifteen years of almost continuous infection, appear to be in good physiologic state. Some authorities, however, believe that the reticulo-endothelial system becomes exhausted, a theory which would explain patients' poor resistance to other infections.

EVOLUTION AND PROGNOSIS

When reinfection occurs, the course of the disease may be indefinitely prolonged and many natives remain infected throughout their lives. In any case, fairly active infection among them lasts from ten to fifteen years. On the other hand, a patient who is not reinfected gets rid of the disease, with or without therapy, within one to two years for *Pl. falciparum*, within two to four years for *Pl. vivax*, and sometimes within an even longer lapse of time for *Pl. malariae*, from ten to twenty years (Bastianelli) and even twenty-one years (Shute).

These occasional cases of reported delayed relapse must be put to the test of careful microscopic examination. It has been said that longstanding cases of malaria are easily subject, when a cold is caught, to pseudo-pyrexial attacks whose character is mostly subjective.

The prognosis depends on the type of infection. It is favorable in the seasons and areas when and where *Pl. vivax* or *malariae* are the only ones known. These forms can produce cachexia but are only exceptionally responsible for pernicious attacks or hemoglobinuria.

It is serious in regions where *Pl. falciparum* predominates. In this case various social factors are important, and the seriousness of the prognosis decreases, in fact, with the advent of civilization. In the Congo, European mortality has been influenced to a very high extent by chemical prophylaxis and better therapeutic measures. Malaria remains, however, the great cause of morbidity and mortality (or repatriation) among the white population of many colonies. Among Negroes, the prognosis is more uncertain. It seems, however, that, either directly or indirectly, because it prepares the ground for other infections, malaria is one of the important causes of mortality among native children. Blackwater fever and pernicious attacks remain serious complications (25 per cent case mortality).

Number of Parasites and Prognosis: The following results were obtained from observations made in the Malay states, over a total of 750 untreated cases: 675 cases who had less than 100,000 parasites per cu. mm.* showed 2 deaths; 75 cases who had more than 100,000 parasites per cu. mm. showed 11 deaths; cases who had more than 250,000 parasites per cu. mm.† showed 20 per cent of the mortality; cases who had more than 500,000 parasites per cu. mm. showed 63 per cent of the mortality.

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* 2.5 per cent of the erythrocytes on 4,000,000 per cu. mm.
† 6 per cent of the erythrocytes on 4,000,000 per cu. mm.

IMMUNITY: MALARIA AMONG NATIVES

Our knowledge of immunity to malaria is based on a wide and varied series of observations. The examples found among old colonials are instructive in this regard: their history usually included an "acclimatization fever" (primary remittent malaria), then relapses, and eventually after two to three years, one or several attacks of hemoglobinuria. But after that, if by any chance the patient were not dead (the annual mortality reached 80 or 90 per thousand), he showed a certain amount of resistance, but only up to a point. His relapses might just as well have been exogenous (different strains or species) as endogenous in origin. The subject's resistance was due perhaps to greater carefulness, born of experience, but also, no doubt, to a certain amount of immunity. Similar facts are gathered from the observation of natives (especially African). The newborn is usually healthy at birth but becomes infected sooner or later, the lapse of time depending on the local density of the Anopheles. According to Van Nitsen's observations in the Katanga, the beginning of the infection would be unobtrusive in 74 per cent of cases. This might indicate a passive type of immunity of maternal origin. Soon, repeated infections occur, whether of the same or of other species. However, in these cases of double infection, *Pl. vivax* and *Pl. malariae* are the first to disappear, and *Pl. falciparum* predominates. The parasite rate (calculated from the number of persons showing parasites in their peripheral blood) reaches a maximum within a period which varies with the area, usually between two and five years. It then decreases with age, at the same time as the parasites decrease in number. As Schwetz pointed out, around two or three years of age the figures for positive results are approximately equal to one another, whether obtained by the thick drop or the thin smear method. On the contrary, a few years later, a thin film often gives a negative result, while the corresponding thick drop shows scanty parasites. The clinical manifestations follow a parallel trend: severe up to five years, and even fairly frequently fatal, they become more benign with age. The adult no longer exhibits clinical symptoms, but does not get any further than a state of "premunition," or, better, of tolerance, rather than of true immunity. It must still be pointed out that this immunity is at first "antitoxic" rather than antiparasitic. Negro children may harbor a considerable number of parasites, while remaining apparently fever-free. The same thing can be observed among Europeans. In the early stages of artificially induced *Pl. vivax* infection, when the fever is still remittent, Swellengrebel and de Buck place the pyrogenic limit between 100 and 900* parasites per cu. mm., while this figure becomes 4,000 to 12,000 when the attacks become more typical; it varies between 1,000 and 80,000 for delayed relapses. Comparable figures for quartan fever are similar: 14 to 560 parasites/cu. mm. in the beginning, 1,600 to 12,500 later. Bastianelli makes the same statement: "A time comes when the fever ceases; there may be then 500 parasites /cu. mm., whereas in the early stages, 10 parasites were enough to cause fever. The patient becomes tolerant as far as the fever is concerned, but keeps the parasites."

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* Much lower figures are accepted, as low as 10 per cu. mm.

Trials among cases of general paralysis also showed facts suggesting an immunity mechanism. It is observed that patients from endemic areas are difficult to infect, so much so that other methods must, perforce, be used. James and others noted experimentally that a patient allowed to go through the whole of his infection, including the late tenth month relapse, showed little receptivity to reinfection. He exhibited a prolonged incubation period, few pyrexial attacks or even remained totally unaffected. Protective properties have been attributed to the serum by Kauders. This immuntiy is limited to the species and even to the strain. Working on general paralytics, Swellengrebel and de Buck found that all Dutch strains of *Pl. vivax* are homologous, but that, on the other hand, they afford incomplete protection against Madagascar strains, and none at all against *Pl. malariae*. Moreover, experience shows that this immunity is also developed by the European in Holland. At Wormerveer, there are 180 cases per thousand among children and only 40 among the adults.

The splenic rate lags behind the parasite rate. The "endemic" index combines both of these.

Experience acquired by various mining companies showed that the natives from the African high plateaus, when brought to working centers situated at low levels, develop there a severe type of malaria characterized by severe forms, pernicious attacks, hemoglobinuria. This fact must be attributed to their lack of premunition. This would tend to prove that there is no racial immunity factor.

Provocative Methods: The passage from latent to active malarial infection occurs in various fortuitous circumstances: fatigue, exposure to cold, trauma, labor, vaccination, therapeutic use of 914,* etc. Provocative methods are sometimes used as diagnostic or therapeutic measures: protein shock, cold showers, and, most efficacious of all, the injection of 1 mg. of adrenalin: the spleen contracts and parasites appear in the blood within one to two hours (the blood is examined every one-half hour). The foregoing must be considered if mistakes are to be avoided after surgical interventions, etc., and even more if agues are to be prevented by appropriate therapy (i.e., before an operation or labor).

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* 914, slightly curative for *Pl. vivax,* can on the contrary provoke a *Pl. falciparum* attack.

DIAGNOSIS

Clinical diagnosis may be very easy if tertian or quartan intermittence is present. The characters of each attack may be most suspicious too: agues developing in the daytime and not in the evening, abrupt onset, intense shivering, very pronounced sudation, absence of visceral localization. An intermittent or markedly remittent quotidian fever makes the diagnosis more difficult. It is more particularly reminiscent of deep abscesses, infections of the biliary and urinary tracts, tuberculosis, etc. Even more difficult to diagnose are the subcontinuous fevers seen at the beginning of the illness (mostly in *Pl. falciparum* infection). Influenza, dengue, meningitis are often considered. During the eight months of the campaign in the Solomon Islands, many cases of "masked malaria" were observed. The diagnosis made varied from angina pectoris, coronary thrombosis, and paroxysmal tachycardia to virus pneumonia, pleurisy, lung abscess, gastric ulcer, cholecystitis, arthritis, meningitis. The shivering, the microscopic examination, and the results of treatment proved decisive factors for the diagnosis. In fact, the clinical diagnosis must be completed by *microscopic examination.* This alone decides. The safest technic is that of the thick drop. Thin films, however, are not to be neglected, as they give more precise information about the species concerned and the number of parasitised red cells. (The staining is done with Giemsa or Wright's.) Examination of fresh specimens is not easy to do in current practice. The results of the thick drop technic must be carefully interpreted among native populations, as these so often present symptomless infection. Here again, a thin film shows more clearly the extent of the infection. In doubtful cases, specific therapy is always legitimate and may prove useful, but must not be allowed to take the place of a complete examination.

So far, specific serologic reactions have not been used to any great extent in practice. Recently, however, Coggeshall and Eaton, Dulaney and Stratman-Thomas (1940–1942) attributed a certain value to positive responses (antigen of *Pl. knowlsi*). Nonspecific reactions (sero-flocculation test of Henry) have shown some success, but are patently inferior to detection of the parasite. Such reactions can be observed in various infections: kala-azar, leprosy. Up to this day, blood chemistry is unable to give us any specific information. The secondary anemia shown by hematologic examination carries no diagnostic weight. On the other hand, a rather low leukocyte count, associated with a definite monocytosis (15–20 per cent) is very suspicious. Pigment-containing leukocytes are pathognomonic. The finding of parasites (with the help of provocative measures such as adrenalin, if required) remains an essential for diagnosis.

Therapeutic Trial as a Means of Diagnosis: This method is only too much a temptation for the always overworked practitioner. This is especially true in hot countries, where malaria appears as the predominant cause of fever. It is inadvisable except in cases where circumstances do not permit microscopic confirmation of the diagnosis. For, whether the patient dies or recovers within the next three or four days, his illness remains undiagnosed, and it will be impossible to know in the second alternative, whether to carry on with treatment or not. The diagnostic value of specific therapy remains confined to the instances when it fails. It can be put down as a principle that any fever which resists longer than five days to active antimalarial treatment is not malaria. In such a case, it is necessary to modify both diagnosis and treatment, and not to keep on for a month (as is often seen) with the whole range of antimalarial drugs in all their forms and with all their possible modes of use. Before reaching a negative conclusion, the use of the parenteral way is imperative as cases of nonintestinal resorption have been described, especially with atabrin (Yudkin, 1946).

TREATMENTS

1. *Quinine*

Quinine is the oldest of the specific antimalarial drugs. *Cinchona* trees originated from the Andes, but are mainly cultivated in Java. In the Belgian Congo, successful plantations have been made in the Kivu (*C. ledgeriana*). South American production began to draw attention again after the occupation of Java by the Japanese. The alkaloids are found in the bark (tannates 5 to 18 per cent) and include quinine and its isomer quinidine, cinchonin and its isomer cinchonidin, and in addition an amorphous residue called quinoidin. Quinine, the most used of these compounds, is especially abundant in *C. ledgeriana* (a rather delicate tree with a yellow bark) where it constitutes up to 70 per cent of the total weight of the alkaloids. It is not so abundant in *C. succirubra* (a hardy species with a red bark) in which it represents only about 30 per cent of the alkaloids.

Cinchona Febrifuge, Quinetum, Totaquina: These are whole alkaloidal extracts which are standardized at 70 per cent crystallized alkaloid, of which 15 per cent is quinine. These extracts are active. Their importance lies mainly in their industrial preparation, which allows the utilization of the residues of extraction, or the use of cinchona of low alkaloid content. The cost of production is vastly below that of quinine.

Pharmacognosis: Quinine ($C_{20}H_{24}N_2O_2$): The structural formula contains a quinoline ring and another heterocyclic ring called quinuclidine, and many substitution groups including one methoxy (replaced by H in cinchonine), and a vinyl group (unsaturated, hydrogenated) in hydroquinine (a synthetic substance which is also active). It is a "diacid" base (called also "dibasic"). Its salts are of the Q—HCl or Q $(HCl)_2$, and of the $Q_2H_2SO_4$, $7H_2O$ or Q—H_2SO_4, 7 H_2O types. The diacid salts are much more soluble, and of course a little poorer in quinine base than the monoacidic ones. They are usually slightly acid to litmus, while the monoacid salts are neutral in solution.

Principal Salts

	Formula	Percentage of quinine base	Solubility in water
A. *Monoacids:*			
Monochlorhydrate	Q—HCl,2 H_2O	81.7%	1/34 (neutral solution)
Bromhydrate	Q—HBr,1 H_2O	76.6%	1/55 (" ")
Formiate		87.5%	1/19 (" ")
Sulphate	Q—H_2SO_4,7 H_2O	72.8%	1/800 (" ")
B. *Diacid:*			
Bichlorhydrate	Q—$(HCl)_2$	74%	1/0.7 (acid solution)
Bisulphate	Q—H_2SO_4,7 H_2O	59%	1/12 (" ")
C. *Low soluble*, and therefore tasteless:		31%	1/480
Tannate			
Ester ethylcarbonate (Euquinine) Carbonic ester (Aristochine)	These esters are nearly insoluble		

Practically speaking, the monochlorhydrate is the best of these salts. The neutral sulphate is usable for nonurgent cases and is less costly. The formiate is often utilized for injections. Diacid salts may be useful for the preparation of concentrated solutions, which can then be taken orally, in drops (children), or be diluted for intravenous injections. The tannates and the esters are not very useful. If they are given, the dosage must be two or three times that of the usual salt. (150/100 for Euquinine; 300/100 for the tannate).

The Belgian Pharmacopeia contains the following compounds (Ph. B. IV): Quinidine sulphate. Quinine ethylcarbonate. Quinine bromhydrate (Q. HBr). Quinine chlorhydrate (Q. HCl). Quinine sulphate, (Q_2—H_2SO_4). The supplement introduces in addition: Quinine bichlorhydrate ($Q=(HCl)_2$), Quinine bisulphate, (Q—H_2SO_4), and finally Totaquina.

Pharmacodynamics: Absorption in the digestive tract is rapid, most of the dose being absorbed within six hours. Its presence in the blood is rather short-lived. The residual concentration is, according to some, higher in the erythrocyte but others deny this. Most of the excretion takes place through the kidneys (also within six hours).* Three or four per cent is excreted by the bowel, other routes (saliva, milk) being negligible. An important proportion is metabolized and its fate is unknown. Absorption is sensibly slower when it is given by the intramuscular route than when given orally. This can be attributed to local necrosis. A single dose of 500 mg. maintains a concentration between 0.15 and 1 mg. per 100 cc. of plasma during the next twenty-four hours. With a dose of 1–2 Gm. this concentration varies between 1 and 3 mg. Quinine exerts a toxic action on protoplasm in general by the inhibition of ferments; hence, too, its antithermic action, and in large doses its depressing action on the nervous system (respiratory paralysis), and the striated muscles, including the myocardium. On the contrary, the smooth muscles of the spleen and uterus are stimulated. The prothrombin level is said to be lowered.

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* The reactives of Tanret and of Esbach precipitate the alkaloid. The precipitate is solved by heating and is therefore easy to differentiate from albumin.

Toxic effects include tremor, faintness, buzzing in the ears (750 mg. is enough), excessive menstrual flow, stimulating action on the uterus, amblyopia (in large doses), sometimes deafness. Death occurs with about 15 Gm. Children are less sensitive to the drug. Idiosyncrasy is met with here and there but can be overcome by "vaccination." At one time it was the practice to test the tolerance in future colonials. This became unnecessary since the discovery of the synthetic chemical drugs.

Posology: In general, a dose of 20 to 30 mg./Kg. body weight is sufficient for an adult with ordinary attacks. This means in practice a daily total of 1.25 to 2 Gm., taken in three to five divided doses. Larger doses up to 3 to 4 Gm. are prescribed in some severe cases, but they are not always well tolerated, and it is probably better in such cases to use a combined treatment with quinine and atabrin.*

Children can tolerate large doses: 30 to 40 mg./Kg. body weight, and even more. The treatment, started at the ague stage, is continued for seven days and followed by six weeks of a consolidation cure: four days of treatment a week with the normal dose (let us say 1.5 Gm.), then three days a week, then two to the end. Nowadays, we usually prefer to give one week's rest after seven days' treatment, and to carry on with atabrin or quinoplasmin.

Administration. The *oral route* is the best. The powder as such, or the solution has a very bitter taste. Quinine can be given in: (1) cachets, or better, gelatin capsules (these must be filled by the chemist); (2) good quality tablets, i.e., soluble or at least crumbling in water.

Parenteral route: Must be reserved for special cases, either severe ones with repeated vomiting, or to rebellious patients, difficult children, etc. Injections are also necessary in subjects who do not eliminate the quinine through the urine after oral administration. This can be checked by the reactives of Tanret or Esbach. It will soon be possible to return to oral treatment. Ampules prepared by reliable firms must be used. The subcutaneous route is to be condemned (an eschar is easily produced if the solution has a concentration above 5 per cent). The intramuscular route allows the use of 20 per cent solutions. Strict asepsis is essential. The production of a suitable culture medium through local tissue necrosis is the likely explanation of the gravity of the abscesses following quinine injections. The blood vessels and the course of the sciatic nerve must be avoided. The intravenous route must be used with care. It must be reserved for severe cases. Do not give more than 600 mg. in 200 to 400 cc. of normal saline, and inject slowly, after first giving adrenalin.

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* Rasquin observed a total amaurosis accompained by deafness, after 4 Gm. These effects lasted four days, and a persistent hemeralopia remained.

Administration to children: The rectal route is not sure. It is better to give orally solutions containing 10 mg. per drop. The following is a formula often used in the Congo:

Monochlorhydrate	244 Gm. 500
H_2O	160 cc.
HCl (pure)	57 Gm. 60

Mix: Heat in the hot water bath until dissolved.
Once the solution is cold, add:

H_2O	500 cc.
Ether-alcohol	50 cc.

Complete to 1.000 cc. Keep in brown glass. Yellow solutions must be rejected One drop of this preparation=10 mg. of *alkaloid.*

If necessary use ampules, whose content per drop is easily estimated.

An oily suspension of crystallized salt can also be used, a few drops to be taken in orange juice or syrup.

Therapeutic action: The fever disappears from the third to the fifth day, and the trophozoites from the third to the fourth day. (*Pl. falciparum* is slightly more resistant than the others.) The gametocytes of *Pl. malariae* and *vivax* disappear, but not those of *Pl. falciparum*, which remain capable of evolution. Experiments made by various British authors on cases of general paralysis inoculated with malaria by means of mosquitoes showed that the sporozoites too are resistant. Quinine is essentially a schizonticidal. A more definite action on the merozoites has not been demonstrated. The exoerythrocytic forms too seem to be very little affected.

Relapse: Quinine rarely acts as a therapia sterilisans, even when the prolonged scheme of treatment detailed above is applied. With *Pl. vivax* or *malariae* the relapse rate is about 50 to 70 per cent, with *Pl. falciparum* 20 per cent. At any rate, these relapses respond to treatment and the patient becomes cured in the end. From this point of view, a consolidating treatment with Plasmoquine appears to be an advantage.

Mode of action: The toxic action of quinine on protozoa, in vitro, had been observed before, but similar concentrations cannot be expected in man. Moreover, Mühlens and Kirschbaum demonstrated that blood to which quinine had been added to a concentration of 1/5000 remained infectious after 12 hours' contact at 37 C. Therefore the action of quinine is either a direct one, with an unknown intermediary metabolism, or an indirect one. The latter view is upheld by various authors and is in accord with the slowness of the cure. Others admit a double action: at first a direct one, the liberated antigens then stimulating the organic defenses. It seems that the spleen is indispensable to that mechanism in man: its absence (congenital or surgical) is said to have caused disasters. The chemicotherapeutic action would be more certain when the parasites are present in the blood (hence the usefulness of provocative methods).

2. *Plasmoquine, Pamaquin,* Praequine*

Synthetic derivative of quinoline (heterocyclic nitrogenous compound corresponding to naphthalene, which is also found in quinine), used almost exclusively as small tablets taken by mouth. The use in injections seems illogical.

Dosage: Up to 1 mg./Kg. pro die has been given. But this dose is often ill tolerated, and has been brought down to 0.5 mg./Kg. In practice, we use 10 mg., three times per day, either twice a week, or repeated daily for three to four days. It is given after the meals, with sodium bicarbonate.

Toxic effects observed: Gastric and cardiac disturbances, cyanosis (methemoglobinemia), rarely methemoglobinuria or serious symptoms (toxic anemia). The child often tolerates the drug better than the adult. The association with quinine seems well tolerated, but that with atabrin should be definitely discouraged. On the other hand, the drug can be given after a course of atabrin, with a two-day interval.

Therapeutic action: Plasmoquine acts on the schizonts and gametocytes of *Pl. vivax* and *malariae,* and hence on the fever. With *Pl. falciparum,* the action on the schizonts and the pyrexia is weak, but the action on the gametocytes is powerful. The dose is 20 to 30 mg., two to three times a week. In toxic doses, the drug is a true, causal prophylactic.

Quinoplasmine is a combination (Bayer) of 300 mg. of quinine with 10 mg. of plasmoquine, which can, of course, be prescribed magistrally. Mühlens used to prescribe 3 to 4 tablets a day for twenty-one days in succession. We use shorter courses (eight to ten days), which are useful after treatment with the other compounds. Quinoplasmine acts very favorably on *Pl. vivax.*

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* Pamaquin naphthoate contains less active substance than plasmoquine dichlorhydrate. It should, therefore, be given at approximately double dose.

The indications for plasmoquine are actually rather few: as a consolidation treatment and as a gametocide after the use of quinine or atabrin, 10 mg., two to three times a day for three to five days (the course must be carefully watched). Plasmoquine (30 mg., twice a week) and quinoplasmine are mainly used after atabrin (and not concurrently) if crescents remain visible in the blood.

3. *Atabrin* (Quinacrine, *France;* Mepacrine, *England*)

Synthetic derivative of acridine (heterocyclic nitrogenous compound corresponding to anthracene.)

Pharmacology: It is a soluble yellow compound which is easily absorbed (demonstrable in the urine after an hour). It is eliminated in the urine and in the feces over a rather long period. Experimentally, intoxication can be obtained through retention. This has been seen in animals (spleen, liver, kidneys) after oral administration. Atabrin has a dilating action on the blood vessels, including the coronary arteries; in large doses it can cause heart-block or fibrillation (ventricular).

Posology: For adults, the usual dose is 100 mg., three times a day, for five to seven days in succession (taken after meals, with large fluid intake). For children:

Under 1 year..........	50 mg. in 3 divided doses
From 1 to 4...........	100 mg. " " " "
From 5 to 8...........	200 mg. " " " "
Over 8 years...........	300 mg. " " " "

At present there is a tendency to raise the "loading" dosage, and up to 900 mg. have been given on the first day, the doses being reduced to 300 mg. (in three divided doses) for the next six days. An initial strong dose has the advantage of rapidly achieving the effective plasmatic concentration ("fasting concentration") of at least 30 γ per 1,000 cc. and ordinarily of 50. This is obtained with the new method in twenty-four hours instead of forty-eight. The methane-sulphonate or atabrin prepared for injection (musonate) is preferably given by the intramuscular route. The dose corresponds to 200 mg. of atabrin and can be repeated after eight hours. Atabrin dichlorhydrate can also be injected (200 mg. intramuscularly). Intravenous injection is not advisable (in any case, 100 mg. is the maximum at any one time for a repeatable dose). In children under one year of age, the intramuscular injection (50 mg. die divided in two doses) must be regarded with care.

Toxic Effects: The yellow coloration of the skin must be noted, but it has no serious significance. Beyond that, the drug is usually well tolerated. Contrary to quinine, it does not seem to precipitate the appearance of blackwater fever. Twenty-five grams taken at once did not cause death—only repeated vomiting. Symptoms of cerebral excitement, psychoses, convulsions, etc., and occasionally fatal collapse have been noticed, more particularly in Asia, in weakened individuals. The interpretation of these facts is rather delicate. As Mühlens observed, these cases may be the outcome of malarial states no longer responding to overdelayed treatment. It has, however, been established that cerebral excitement and sometimes other mental disturbances can occur. Gastrointestinal troubles have been described, as well as occasional dermatitis of a type recalling lichen planus (idiosyncrasies).

Lichen planus due to atabrin: This dermatitis has been observed rather frequently in the Pacific area. In fact, the morphology of the eruption is rather variable. Next to papulous lesions similar to lichen planus, desquamating erythemata, vesicular lesions or even bullous and ulcerous lesions have been observed. More delayed lesions of the verrucous type have also been noticed. Secondary infections with staphylococci or streptococci have aggravated the condition, with resulting atrophic or pigmented sequellae. The lesions are more especially found on the hands including the palms, the soles of the feet, the arm pits, and the genitocrural region. The relation between atabrin and the here-mentioned dermatologic condition seems well established. The interruption in the use of the drug has a favorable effect. The prognosis is reserved. Exfoliative dermatitis is rare.

The association of atabrin and plasmoquine is to be rejected, as it often causes symptoms of malaise.

Therapeutic Results: Atabrin exerts an action of the same order as quinine (schizonticidal), but is probably a little more efficacious with a lesser relapse rate (10 to 20 per cent). Both fever and parasites disappear after three to four days.

The mode of action is possibly direct. Fluorescence microscopy shows the fixation of the compound on the parasites and subsequent alteration of the latter. The drug acts even in cases of blockage or so-called blockage of the reticulo-endothelial system associated with splenectomy. These facts are not absolutely decisive in favor of direct action.

4. *Paludrine* (N_1-p-chlorophenyl-N_5-isopropyl biguanide)

This preparation has been introduced commercially quite recently. It seems to be a very valuable acquisition. Its toxicity appears to be weak: up to 1.5 Gm. a day has been given, and a 1 Gm. dose has been repeated for fourteen days. The therapeutic dose would be 100 mg. three times a day for ten days, followed by a single dosis of 100 mg. once a week for four weeks. A 100 mg. dosis of paludrine has equally been given with 10 mg. of plasmoquine, three times a day for ten days. Such a treatment may prevent relapses in cases due to *Pl. falciparum.* It must be continued with a dosage of 100 mg. twice a week in cases due to *Pl. vivax.*

Paludrine has a wider action than quinine or atabrin. Not only are the trophozoites killed but also the pre-erythrocytic forms, including possibly the sporozoites (H. Fairly). This fact is clearer for *Pl. falciparum* than for *Pl. vivax.* The gametocytes of *Pl. falciparum,* under the action of paludrine, interrupt their development. The toxicity of the drug seems negligible.

Its clinical action, however, is so slow that the use of the older products is preferable in serious conditions of the disease.

5. *Chloroquine* (Aralen)

7-Chloro-4,4′ diethylamino-1-methylbutylaminoquinoline has an action similar to that of atabrin. It is prescribed at the following dose: *Pl. falciparum,* 1 Gm.; then, after six to eight hours, 500 mg.; and 500 mg. the second and third days. The cure seems radical in twenty-four to forty-eight hours for the fever, and forty-eight to seventy-two hours for the parasites (total dose, 2.5 Gm.).

Pl. vivax 500 mg.; then, after four hours 500 mg. again; and then 500 mg. the second, third, and fourth days (total 2.5 Gm.). Relapses are possible here.

The toxicity is slight and not characteristic.

6. *Pentaquine* (methoxy-8-5 isopropylamino-quinoline)

This preparation is closer to plasmoquine, with the same toxicity qualitatively but reduced to the half quantitatively (abdominal malaise, methemoglobinemia). Associated with quinine, its action on *Pl. vivax* is good: 60 mg. of the base (80 mg. of diphosphate) associated with 2 Gm. of quinine daily for fourteen days cures the infection. This dosage is divided in several daily intakes. The product does not seem to be definitely introduced in the therapeutical arsenal.

GENERAL SCHEME OF TREATMENT

In the light of experience acquired to date, and more particularly during the 1939–1945 war years, it appears that quinine and atabrin are about equal in efficacy. If 300 mg. of atabrin are a sufficient daily dose for light infections, serious cases require more, at least on the first day. In urgent cases (coma, etc.) quinine still seems to be preferred. The following are schemes of treatment inspired from military experience:*

1. *Uncomplicated Cases, without Vomiting:*

Atabrin chlorhydrate	200 mg.	five such doses at six-hour intervals.
+ Sodium bicarbonate	1 Gm.	
Sweetened drinks	200–300 cc.	

Then 100 mg. three times a day for six days (after meals).

Total: 2.800 Gm.

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* One cannot compare a resident living a normal life with a soldier in the field or an explorer.

or Quinine chlorhydrate, 500–650 mg., three or four times a day (after meals) for seven days. If the infection is extremely severe, up to 3 Gm. can be given in the first two days (rarely necessary).

In old malarial cases, atabrin will be given for preference, to lessen the danger of hemoglobinuria. If it is wished to give plasmoquine, 10 mg. can be prescribed two or three times a day for four days, but only after treatment and while a careful watch is kept. Or else, three tablets of quinoplasmine can be taken for a period of eight to ten days after atabrin treatment. One gram of sodium bicarbonate should be prescribed with the plasmoquine.

2. *Cases with Vomiting, or Obstreperous Patients, Children, etc.:*

(a) Injection of 750 mg. to 1 Gm. of quinine, intramuscularly and with strict asepsis, far from the sciatic nerve (the ampules must come from a reliable firm). This injection can be repeated two or three times at eight-hour intervals. It will then usually be possible to carry on orally, preferably with atabrin, for six days (300 mg. per day).

(b) Intramuscular injection of atabrin chlorhydrate or musonate: 400 mg. are given in two separate injections, each with 5 or 7 cc. of distilled water. The 200-mg. injection can be repeated once or twice at six- or eight-hour intervals. As soon as possible, the treatment by oral route is resumed with ordinary doses (a 1 Gm. total in the first forty-eight hours).

3. *Severe Cases:* Coma, algid states, high proportion of parasitised corpuscles (10 per cent or more). Inject intravenously 600 mg. of quinine chlorhydrate in 200 to 300 cc. of normal saline. The injection must be done slowly (with adrenaline at hand). Repeat every six to eight hours. As soon as possible, resume oral treatment.

4. *Pregnant Women:* Quinine exerts an oxytocic action only toward the time of labor, and pregnancy as such is not a formal contraindication to its use. Malaria is certainly more liable to bring on abortion than quinine. Atabrin, too, has some pharmacologic action on the uterus, either isolated or in vivo. In practice, however, it seems that it can be prescribed without fear to pregnant women, and more safely than quinine.

Other Therapeutic Agents

Arsenicals (arsphenamine, acetphenarsine), in spite of some action against *Pl. vivax,* no longer deserve to be used. The combination with quinine produces a compound which can be used in some chronic cases (quiniostovarsol, quinogoyl). It is better, however, to prescribe the two drugs in isolation, at will. Methylene blue (active against *Pl. malariae*) is no longer much in use. Adrenalin (according to Ascoli) would exert a favorable action in chronic cases with splenomegaly, when administered intravenously in doses gradually increasing from 0.01 to 0.1 mg. over a period of twenty to thirty consecutive days (2–4 mg. total). It would, however, be advisable to use the specifics in conjunction with it. The sulphonamides have not yet been introduced on a practical basis, but have been shown experimentally to exert a certain activity.

SYMPTOMATIC TREATMENT

A simple attack needs only ordinary care: hot-water bottles, blankets, avoidance of abrupt chills. Calcium gluconate has been advocated to end the shivering (Santiago, Stevenson). Do not abuse sedatives (an ice-pack on the head is preferable). In case of hyperpyrexia, use physical methods of cooling, such as wet sheets, baths, etc. In case of bacterial superinfection, there is no incompatibility between sulfonamides and quinine or atabrin.

Diet: Must be substantial once the attack is over. Give chlorhydric acid and vitamin C. Cerebral cases need feeding through a nasal catheter, or even administration of fluids through the parenteral route.

Vomiting: Give pieces of ice to suck, chloroform water, and aerated drinks, in small sips. Inject glucose solution. Sometimes morphia with some atropine is useful.

Circulatory Failure: Requires analeptics.

Coma: Calls for lumbar or occipital puncture, and intravenous quinine.

Anemia: A spontaneous cure is usual. Iron and liver extracts can be used.

Chronic Malaria: The patients need rest, a nourishing diet to build them up, and antianemic medication. Atabrin will be used as a specific, at least in the beginning, as there is less risk of causing hemoglobinuria.

PROPHYLAXIS

Many authors agree that malaria is an "indoor" disease (just as African Trypanosomiasis is an "outdoor" disease), acquired in the houses. This may be true for Africa, at least for *Anopheles gambiae*, whose habitat is definitely indoors, but it does not apply to other regions of the world (notably the Far East) or to other Anopheles. Thus the *A. culicifacies*, *maculatus*, and *minimus*, which are found respectively in Ceylon, in Malaya, and in the Philippine Islands, where they are the most important vectors of malaria, as well as *A. albimanus* in Central America, live essentially in the open and are found only rarely indoors. We have only little knowledge of malaria in high countries, but we may wonder whether transmission in such areas does not occur at the bottom of the valleys near the larval breeding grounds (Vincke and Jadin in the Ruanda). We can never sufficiently emphasize, in such an important matter as prophylaxis, the dangers of generalization in anything pertaining to malaria.

Climate is one of the chief epidemiologic factors. Temperature and the degree of moisture are the most important elements. In the temperate zone, the disease disappears in winter. This used to be explained by the fact that anopheles hibernated in the cellars, and could cause fresh infections in spring. Swellengrebel and his collaborators have since demonstrated that the sporocysts degenerated during hibernation. Dutch authors think that the springtime malarial infections found in Holland are acquired during the previous autumn, and exhibit a long incubation or latent period during the winter. Estivo or estivo-autumnal attacks are due in Southern Europe to infections acquired during the summer months themselves. In tropical regions, malaria reaches its fastigium at the beginning and at the end of the rainy season, and it regresses during the dry season. Owing to the lowering of the temperature it entails, high altitude limits the incidence of malaria, either by keeping away the actual vectors, or by inhibiting sporogony. In India and in Africa endemic malaria is not found much higher than 2,000 meters.

In Africa, *A. gambiae* and autochthonous cases or malaria have been reported around Addis Ababa at 2,450 meters (Martin, 1942), and in Kenya at altitudes between 2,300 and 2,600 meters (Garnham, 1945). In India, *A. wilmorei* and *A. plumbeus,* with rare cases of malaria, are found in the Himalayas at an elevation of 2,500 meters. The highest so far reported malaria, *A. pseudopunctipennis,* occurs in certain high valleys of the Andes, above 2,600 meters in the Cinti Valley of Bolivia (Hackett, 1945). Aberrant malaria may occur at even higher altitudes in the vicinity of thermal springs (Ecuador and Bolivia between 2,600 and 2,700 meters).

The nature of the soil, its permeability, and its exposure to the sun, condition the dispersion of malaria. Man by his deforestation, his cultures, his drainage and irrigation works often creates favorable sites for the development of Anopheles which will prove good vectors and disperse malaria.

With such variable factors as the species of Anopheles (see etiologic section), the climate, the nature of the soil, etc., it is obvious that the prophylaxis of malaria is a complex problem. It cannot be conceived along the lines of a rigid scheme, applicable to all countries. Each region must be carefully studied, and the methods to be applied will vary with the circumstances. In Brazil, the destruction of the adult Anopheles alone, by means of Pyrethrum spraying of the dwellings, was enough to obtain total eradication of *A. gambiae.* In other places, economic and social development succeeded in eliminating the disease (lower Belgium). Our present means of fighting malaria are such that we can from now on suppress it within a short lapse of time in well-defined regions.

When establishing plans for the fighting of malaria, the hygienist will first have to determine the degree of intensity and the repartition of malaria in the region of which he is in charge, by means of the various epidemiologic indexes. Then he will have to determine the particular areas of the region where the antimalarial measures will have most chance of being efficacious. This will depend on the economic factors as well as on the endemicity. He will then be able to decide which methods will be most appropriate to the local conditions. These methods are varied and numerous. They are related to the three main elements of the problem: the infected man, the mosquito vector, and the uninfected man.

(1) *Reservoir Hosts*

With the exception of the surely negligible part played by the anthropoid apes, the reservoir of malarial infection is exclusively human, and is, in fact, constituted mainly by the natives. In some cases, it is possible to isolate them more or less completely. In endemic regions, it is desirable to separate the native villages from the centers inhabited by immigrants by a distance well above the normal flying range of the Anopheles. Unluckily, economic circumstances make it difficult to apply this measure. In regions where malaria is only moderately endemic, it is logical to reduce the reservoir by therapeutic measures. Thus, quinine has been largely distributed in some regions of Algeria. Plasmoquine too, being most indicated owing to its gametocidal properties, has been freely given to the Nile delta population. The new antimalarials and particularly paludrine, which is active when the doses are given at widely spaced intervals, will be usable for the same purpose. Such methods, however, are applicable only in regions which are reasonably developed from the economic standpoint. Moreover, it is difficult to do more than lessen the prevalence of the disease by such means.

(2) *Destruction of the Anopheles Acting as Vectors*

This can be carried out in many ways:

(A) Destruction of the breeding grounds (adults and larvae):

(i) This requires a considerable amount of public works to be undertaken in close collaboration between the engineer and the hygienist: clearing and straightening of the river edges, filling in of swamps and ditches, superficial and deep drainage, building of a system of weirs, periodic drying off of irrigated fields, changes in the water level of dammed reservoirs.*

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* These methods were used in 1902 in Malaya by Watson (whose name they still bear); then in 1904 by Gorgas, at the Panama canal. Until recently they were at the base of any antimalarial campaign. Now, however, new fighting methods, such as the possible destruction of the adult Anopheles, will more and more tend to take the place of the large-scale cleansing schemes which always prove very expensive. However, engineers and agronomists must take the advice of the experts in antimalarial

(ii) It implies, too, a sanitary police keeping continuous watch on household water collections, filling in road puddles and garden holes, keeping an eye on vegetable receptacles (hollow trees, cup-shaped plants), and forbidding the abandonment of any recipient on the allotments (bottom of broken bottle, empty tin, etc.). This type of supervision must be organized in all human concentrations in hot climates. Moreover, it is also a very efficacious method of fighting other diseases existing in these areas (development of Aedes).

(B) Destruction of the adult Anopheles: (i) Natural means are rarely efficacious (predatory bats, traps, capture by hand).

(ii) Spraying the inside of houses with pyrethrum (100 Gm. of powder for a liter of kerosene, petrol, or turpentine) gave good results in Europe, India, Brazil, and Africa. An endophilic Anopheles such as *A. gambiae* may even totally disappear from a fairly vast area (Brazil) after methodical application of it. The spraying must, however, be repeated twice a week, as pyrethrum rapidly loses its insecticidal properties.

(iii) The insecticide DDT Geigy: dichloro-diphenyl-trichlorethane. It poisons by ingestion but especially by contact, creating a liposoluble combination with the lipoids of chitin and following the myelin sheaths to reach the central nervous system of the insect. It is always fatal for flies and mosquitoes. It is an odorless (does not repel the insects) white powder, nonvolatile, unalterable in the normal range of temperatures, unaffected by light and practically insoluble in water: its action is therefore extremely durable. The commercial product contains only 70 to 77 per cent of the active isomer, the remaining percentage containing the inactive isomers which represent impurities.

After the spraying of the houses, the DDT particles left on the wall remain active for several months. As soon as mosquitoes have come in contact with DDT, they stop biting, fly out of the houses if they are not closed, and die within twenty-four hours. A watery emulsion of a solution of DDT appears the best for spraying smooth surfaces, such as walls covered with oil-paint. On the other hand, a suspension of DDT powder in water is best for porous walls (mud walls, white-washed walls), as water alone enters the wall, while the particles remain on the surface. To obtain an emulsion in water, start from a concentrated solution (e.g., 3.5 parts in weight of DDT for 9 parts in weight of xylol, stirred with 1 part in weight of an emulsive agent, the Triton X-100). Stir 1 part of this concentrated solution with 4 parts of water. A dosage of 2 Gm. of DDT per square meter (i.e., approximately 200 mg. per square foot)

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hygiene regarding drainage undertakings and the construction of waterways and tanks, as well as for new agricultural plans, so as to avoid creating new breeding grounds for the Anopheles. This was done very efficiently in the Tennessee Valley developments (U.S.A.).

reduces the number of Anopheles by 100 per cent, inside the houses, for five months. DDT is also used in "aerosol bombs," which are small contraptions the size of a hand grenade, dispersing a very fine cloud of particles of DDT solution. The mixture contains 1 to 5 per cent of Freon (aerosol). The commercial aerosol bombs usually contain pyrethrum (0.3 per cent of pyrethrine for 3 per cent of DDT) for entirely psychologic reasons (the knockdown action is faster).

DDT, whether as aerosol, or powder, or suspension, can also be used out of doors, by means of a portable apparatus: compressors mounted on trucks or planes, to reach and kill both adults and larvae in the Anopheles breeding grounds. In this case, the application must be repeated every three to four weeks.

(iv) Several new insecticides have been used experimentally recently, such as the British Gammexane (or Benzene Hexachloride) and the American Chlordane, Chlorinated Camphene, Rothane, Methoxy DDT, and Lethane-Thamite. None of them surpasses the DDT Geigy nor even equals its toxicity and prolonged residual effect against the mosquitoes and flies. Gammexane has an unusual and marked toxicity only for ticks and mites. (See further, section on Rickettsial diseases.) Pyrethrum has been favorably associated with piperonyl butoxide as synergist.

Research has been undertaken in some countries with a view to combine the toxic properties of DDT (or of other powerful nonrepellent insecticides) with those of substances designed to attract the Anopheles. We may soon possess perfect insecticides.

(C) Destruction of the larvae:

(i) Natural methods are here numerous and efficient; changing the flora, drying off by means of plants, modifying the amount of cover according to the species of Anopheles (*A. umbrosus* breeds in shaded spots, while *A. albimanus* is mainly met with in open and sunny spots), stirring of the water surface, pollution of the waters, increase or decrease of their degree of salinity (as the various species vary in their requirements), and lastly breeding of predatory species, such as Gambusia, a type of small viviparous fishes which prove very adaptable, extremely prolific, and feed for preference on mosquito larvae.

(ii) The use of *oil* kills the mosquito larvae both by asphyxia (blocking of the tracheae) and by intoxication of the nervous system. At least 200 liters of kerosene per hectare must be used (25 gallons per acre).

Oiling gives the best results on calm water surfaces, containing little vegetable growth and waste. Indeed, it only reaches full efficacy when the whole of the water surface is covered with a film 15 to 20 microns thick. This is harmful for the aquatic fauna, and fishes in particular. To avoid this drawback, the following emulsion has been recommended: 66 per cent kerosene, 0.07 per cent pyrethrine, 33.5 per cent water, and 0.5 per cent lauryl sodium sulphate. This concentrated emulsion is diluted 1 in 10 before use (Guisburg). It kills the mosquito larvae and pupae, but is harmless for fishes.

(iii) *Trioxymethylene* was introduced by Roubaud in 1920. It is the first example of the use of a poison acting by ingestion on the larvae of Anopheles. It is made commercially under the name of Stoxal (Poulenc).

(iv) *Paris green* is a copper aceto-arsenite and is poisonous by ingestion. Therefore, it does not act on the pupae or the eggs of the Anopheles, but only on the larvae feeding at the water surface. In its commercial form, it contains at least 50 per cent of arsenious oxide. The powder is usually mixed with 50 to 100 times its weight of some inert very dry powder such as road dust, and is sown by means of a dusting machine or by plane. It is generally used at the rate of 1 to 5 Gm. of Paris green per 100 sq. meters of water surface.

(v) A powder containing 1 to 5 per cent of DDT, and used at the rate of 125 Gm. per hectare (0.1 pound of DDT per acre) is 25 times more active in killing larvae than Paris green. It is not toxic to fishes at such dose. It can also be used as a 5 per cent solution in kerosene, at the rate of 2 $^1/_2$ liters of solution per hectare (125 Gm.). When the water expanses are exposed to strong winds or invaded by thick vegetable growth, an even repartition will be more easily secured, with the same dose, if 12 $^1/_2$ liters of 1 per cent solution are used.

(3) *Protection of the Uninfected Man*

(A) Choice of housing sites. Houses and tents must be distant from the breeding places, and far, too, from the native reservoir of infection. The distance the Anopheles can travel varies with the species, the nature of the ground, and the strength of the wind. In mountainous regions, altitudes above 2,000 meters are usually safe (see the sections on etiology and transmission).

(B) Mechanical protection of dwellings is particularly efficacious: double doors closing automatically, windows protected by wire-mesh. If not kept in perfect working order, such mechanical means of protection may, however, prove harmful, by allowing Anopheles to get in but not to get out. The protection of beds with mosquito netting is essential in all malarious regions. The best are rectangular in section, follow the edge of the mattress closely and carry at their lower edge a double strip of linen to protect against bites the parts of the body which might come in contact with the mosquito net during sleep. The net should be rolled up in the morning and set up again before dusk. Netting is more pleasant than muslin. In any case, the material must have 7 meshes per cm.

Children up to the age of 7 or 8 are perfectly protected in cots, both strong and light, made of rectangular wooden frames strung on the outside with metallic mosquito netting, and on the inside with wide-meshed wire netting to prevent the skin from coming in contact with the first. The top panel opens on hinges like the lid of a box. To make it easier to transport when traveling, the whole bed may be made of a set of frames which can be dismantled.

The wearing of light boots and long trousers, and perhaps even gloves, affords good protection out of doors or in an unprotected shelter. Headgear provided with antimosquito veil is most useful for sentries.

(C) Domestic fumigation is practiced by the natives, whether intentionally or not. It repels the mosquitoes to a certain extent, but is not of a very pleasant use. Repellent preparations applied to the skin protect for a few hours only. Oil of citronella, or of cedar, and camphor have been practically abandoned. Recently, dimethyl-phthalate has been used: it is effective and does not irritate the skin.

(D) The zoophilic tendencies of some species can be taken advantage of to draw the Anopheles on to domestic animals instead of man. This method proved decisive in some regions (in lower Belgium, *A. maculipennis*, which was a vector of malaria, is now found only in sheds, and mainly in pig sties), and most effective against some species such as *A. hyrcanus*. It is erratic in other places (in Indo China, with *A. minimus*, Toumanoff) and useless for Anopheles of the *gambiae* type.

(E) Individual chemical prophylaxis:

(i) *Quinine:* It has proved its efficacy historically. However, we know now that it really is a therapeutic to the limit. The dose of 1.5 Gm. to 2 Gm. a week divided on three or four consecutive days greatly diminishes the spells. Some prefer to take it on two consecutive days, but this strong dose is somewhat upsetting. Then a very large number of colonials take 400 or 500 mg. daily. This last method has the advantage of presenting less risk of forgetfulness. Children are given corresponding doses. The innocuousness of this method has been established for years.

(ii) *Atabrin:* The use of 100 mg. pro die has come into practice during the last war and has proved more active than quinine. A basic plasmatic concentration (fasting concentration) of 12 to 17 γ per liter must be reached. One takes 100 mg. six days a week, or 400 mg. twice a week, or, finally, a less sure method, 200 mg., twice a week. If one keeps on with the first method for four weeks, after having left the endemic zone one can prevent the appearance of *Pl. falciparum* but not of *Pl. vivax*. To continue this method seems without danger in the limits of present observation. The coloring of the skin is only aesthetically inconvenient. The relation between atabrin and the dermitis reminiscent of the lichen planus is certain. At any rate these accidents are not frequently met with.

(iii) *Paludrine:* According to H. Fairley and colleagues, 1 Gm. of

TREATMENT OF MALARIA (ADULTS)

Drug	Quinine	Pamaquine	Quinine Pamaquine (30 : 1)	Atabrin	Chloroquine	Paludrine
Dose	500–600 mg.	10 mg.	Q.300 mg. P. 10 mg.	100 mg.	500 mg.	100 mg.
Frequency	3 times per day	3 times per day	3 times per day	3 times per day	3 times the 1st day; twice on following days. Total: 2.5 Gm.	3 times per day
Duration	7 days	4 days	8–10 days	5–7 days; Total 2.8 Gm.	3 days	8–10 days
Blood level	3–10 mg./liter	....	....	40–100γ/liter	100–160γ/liter	25–150γ/liter
Toxicity	Light, various disturbances	Notable; digestive and cardiac disturbances; methemoglobinemia	Moderate (control)	Light but digestive disturbances and rare cerebral disturbances	Light (vision-audition)	Very light
Pl. falciparum	Controls	Week action	Cures	Cures	Cures	Cures
Pl. vivax	Relapses frequent	Relapses rare	Cure frequent	Relapses rather delayed	Relapses delayed	Relapses
Suppressive dosage	400–600 mg. daily or 4 consecutive days per week	....	....	100 mg. daily (or 6 days per week)	250 mg. weekly	10 mg. 2 or even 3 times per week
Remarks	(1) Secular experience (2) Not indicated in chronic malaria (hemoglobinuria)	(1) To be associated with quinine (2) Not to be given simultaneously with atabrin (3) Specially active on *Pl. falciparum* gametocytes	The most active treatment against *Pl. vivax*	(1) "Loading dose" increasing the dosage of the first 24 hours (600 mg.) (2) The suppressive "prophylactic" use is responsible for a yellow pigmentation of the skin, sometimes for a bluish pigmentation (nails) and exceptionally for eczematoid or lichenoid dermatitis with possi-	Possibly the best curative treatment	Possibly the best preventive drug. Experience is, however, brief

paludrine three hours before an infection by mosquitoes, or a single 100 mg. dose from the second to fifth day after infection, is a complete causal prophylactic against *Pl. falciparum* (action on the sporozoite or on the exo-erythrocytic cycle). For subjects incurring considerable risk of infection, 100 mg. daily protect them against the infection due to *Pl. falciparum.* For field prophylaxis, 100 mg. twice, or better three times a week is the recommended dosage. Against *Pl. vivax,* this should be continued for some time, the prophylactic action being less complete.

(iv) *Chloroquine:* A dose of 300 mg. per week, taken always on the same day of the week, would give a good protection.

5. BLACKWATER FEVER*

Definition: An acute hemolytic disease accompanied by fever and hemoglobinuria, whose malarial origin distinguishes it from other similar syndromes.

Geographic Distribution: The same as that of *Pl. falciparum* malaria, including Southern Europe and the South of the U.S.A. It occurs frequently in tropical Africa. In European temperate latitudes it is found only among those who have returned from the Tropics.

ETIOLOGY

Certain competent observers have reported the presence of various Leptospirae in cases of this disease but there has been no confirmation of these reports. Other infections would appear to be the reason for their presence. The majority of contemporary authors agree that there is a causal relationship between malaria and blackwater fever. The following facts confirm this:

1. The geographic distribution of blackwater fever is exactly the same as that of *Pl. falciparum.*

2. Both diseases occur with equal frequency among a certain class of patient: male adults living in the bush, e.g., prospectors, hunters, etc.

3. Patients ill with blackwater fever most frequently give a history of previous attacks of malaria, though in certain cases these may only have been larval forms of the disease with only slight fever but with anemia, digestive troubles, etc. Examination for parasites is positive with a varying frequency (40 per cent to 90 per cent according to different authors), but on the second day of the hemolytic attack it often becomes negative. Postmortem appearances are also in accordance with the malarial etiology (Darling). Rhodesian hospital statistics show that of about 3,000 cases admitted with malaria 32 developed blackwater fever, while among about 16,000 admitted for other causes only one developed blackwater fever (Ross).

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* In French: Fièvre Bilieuse Hémoglobinurique. In German: Schwarzwasserfieber.

4. Observation of Europeans shows that at the same time they bring malaria back from hot countries they bring also a tendency to blackwater fever.

5. Malaria therapy, especially with *Pl. falciparum,* has been followed by blackwater fever.

6. Animal experiment shows that *Macacus rhesus* (Maccaca mulatta) when inoculated with *Pl. knowlsi* develops with great regularity a fatal infection very often accompanied by hemoglobinuria. This is independent of all treatment.

7. Lastly, prophylaxis seems to have had the same good effect on both malaria and blackwater fever, making the attacks of both less frequent and less severe. The predominant role of *Pl. falciparum* is also universally admitted. There are, however, a very few recorded cases of blackwater fever, following malaria therapy which are related with *Pl. vivax, malariae, ovale,* and *knowlsi* (in man).

Besides the fundamental part played by malaria, clinical experience shows that there are frequently other predisposing causes which, however, need not necessarily be present. The most important of these are fatigue and chills. These two occasional causes explain the frequent incidence of blackwater fever among subjects leading a primitive life, as well as its recoil from civilized and town life. In addition, the taking of fairly heavy doses of quinine during the course of chronic malaria may be a third predisposing cause. There are hardly any colonial doctors who have not made these observations, the interpretation of which is, however, delicate. Atabrin appears to be less dangerous and therefore more indicated in cases of chronic malaria. The part played by quinine in certain cases of chronic malaria can be cited as evidence. These patients react to each absorption of a moderate dose of quinine by a short febrile hemolytic attack. Sometimes intramuscular injection is tolerated better than oral administration. These repeated attacks due to quinine are usually benign. It must be noted that blackwater fever seems to demand a certain chronicity of the malarial infection which modifies in an unknown way the reaction of the system. It is rarely seen among those with less than one year's stay in the tropics, most commonly among those whose stay has lasted three to five years, and progressively rarer among the older residents. It must also be noted that blackwater fever is not transmissible, either by injection of blood or through the intermediary of a mosquito.

Blackwater Fever in Natives: It is striking to notice the rarity with which this syndrome occurs among the natives of Central Africa who have been infected and reinfected since the first months of their existence. The rare cases seen would perhaps be related to the quinine treatments administered during the course of malarial attacks. Severe cases of blackwater fever have frequently been observed among Africans from the high plateaus who have been transported to lower altitudes. These subjects ordinarily have not developed any resistance to malaria and behave, therefore, like Europeans. It is possible that the attacks of blackwater fever reported among Asiatics, etc., are also due to insufficient immunity. One must not neglect the possibility of the existence of other hemoglobinurial diseases (see below).

PATHOLOGIC MECHANISM

This remains extremely obscure. The old theory of Plehn of a hemolysis in the kidney is no longer accepted. The discovery of hemoglobinemia, sometimes of a relatively high degree (nearly 5 per cent), can be explained only by an intravascular hemolysis, perhaps in the sinuses of the spleen, whose function both as an anti-infective and as a storing of red blood corpuscles is well known. In this case the hemolyzed blood would pass into the circulation only at intervals and this would explain the irregularity of the hemoglobinemia sometimes noted. Even the mechanism of the henolysis is unknown. The presence of hemolysins has not been established but this is not surprising: they can be fixed, as it happens, when foreign hemolysins are injected. Foy and his colleagues (1941–1945) have established that normal blood is rapidly hemolyzed when introduced into patients suffering from blackwater fever. The same rapid hemolysis takes place if the patient's red blood corpuscles are introduced into a normal subject. The first phenomenon seems to presume the presence of free lysins in the plasma, the second of lysins fixed on the corpuscles. The fact that plasma from a blackwater fever patient when introduced into a subject infected with *Pl. falciparum* does not precipitate hemolysis is unfavorable to the first hypothesis. Perhaps some special role may be attributed to the spleen, but the theories put forward are not satisfactory. Maegraeth, Findlay, and Martin (1943) have noted the existence of a tissue lysin (lysolecithin) which would not normally be inhibited in blackwater fever patients.

In any case the hemolysins a frigore, which are characteristic of paroxysmal hemoglobinuria and responsible for the phenomena of Donath-Landsteiner and of Ehrlich (see below) are not present here. Hypocholesterolemia and hyperlactacidemia have been incriminated, without proof, as either predisposing to or causing the hemolysis. So far as quinine is concerned, it is hemolytic only in vitro in concentrations unattainable in vivo—such concentrations as would cause death from cardiac paralysis much earlier. Experiments made by Nocht and Kikuth some time ago show that this alkaloid can upset the balance between heterolysins and antihemolysins, and so precipitate hemolysis. No satisfactory explanation of the genesis of the hemolysins has been given: sensitization to the proteins of Plasmodium would be not unlike *favism* which is mentioned below. The existence of an Rh type antigen in Plasmodium has also been suggested. In this case the disease could exist only in Rh negative individuals.

Gear has recently tried to establish that red blood corpuscles plus the parasites plus eventually a drug can become an auto-antigen producing lysins. Then hemolysins would accumulate in the spleen because of the stasis of blood there, due to malarial congestion. A sudden contraction of the spleen would liberate this lysin and precipitate so intense a hemolysis that the transformation into bilirubin (possible under normal circumstances) would no longer occur and there would be hemoglobinemia and hemoglobinuria. In actual fact all this pathologic mechanism is still undetermined and may perhaps refer to mechanisms varying according to the nature of the hemolytic crisis.

THE BLOOD, THE BILE, AND THE URINE IN BLACKWATER FEVER

Erythrocytes: The disease can begin with a slightly lowered count but there is often an enormous drop. Apart from that, the resistance of the cells is normal, though some autoagglutination and spherocytosis are sometimes reported. During convalescence the usual signs of regeneration are seen. Malarial parasites are usually not very numerous and tend to disappear during the course of the hemolysis.

Leukocytes: There is nothing very characteristic except a monocytosis after the attack.

Plasma: The blood sugar is normal. The cholesterol level is usually low but this commonly occurs in anemia. The alkaline reserve is slightly diminished. Nonprotein nitrogen increases slightly in grave cases and markedly in cases of anuria. The blood bilirubin is always increased (indirect Hymans van den Bergh reaction becoming increasingly positive). The direct reaction is present in certain grave cases with obstructive jaundice. The pigments observed in the plasma are:

1. Oxyhemoglobin.

2. Pseudomethemoglobin, or better, methemalbumin. This substance is derived from the action of hematin on the albumin of the plasma. It is formed in vitro and also in vivo following contact of the plasma with methemoglobin or with hematin. This substance, which is to be distinguished from methemoglobin by its spectroscopic properties, does not pass into the urine. It is not specific to blackwater fever.

3. Bilirubin. Always in considerable excess because of the activity of the reticulo-endothelial system which is trying to dispose of the liberated hemoglobin. A hemoglobinemia higher than 100 mg. per 100 cc. of plasma leads to hemoglobinuria.

As for the methemoglobin, it exists only in the corpuscles and in the urine.

Bile: The bile is rich in bilirubin which can reach many times its normal concentrations.

Urine: In the urine there are present varying amounts of:

1. Oxyhemoglobin.

2. Methemoglobin. These two substances give the urine a color more or less dark (according to the degree of hemolysis) and later becoming like red wine (oxyhemoglobin) but most often brown (port wine) or black (stout) due to methemoglobin.

3. Urobilin but not bilirubin or bile salts except in cases of obstructive jaundice.

4. There is usually a deposit of a brown pigment which is probably acid hematin and is undoubtedly identical with that seen histologically in the renal tubules. Casts are also present.

5. Albumen. This is always present temporarily, becoming absent shortly after the disappearance of the pigment. Bacteria have also been reported in the urine but this has scarcely been confirmed. Red corpuscles are absent, or, more exactly, few in number. Bastianelli has reported yellow grains whose nature is unknown.

PATHOLOGY

Similar to that of malaria with more lesions in the kidneys and nothing else specific.

Spleen: Congestion often associated with necrosis of the lymphoid pulp. A moderate quantity of malarial pigment and abundance of hemosiderin are present. This latter, which gives the Prussian blue reaction, is not in the least specific as it is found in every intense hemolysis and it undoubtedly represents the manner of iron deposit. Phagocytosis of erythrocytes is frequently intensified.

Liver: Congestion, with the gall-bladder distended with thick black bile which is very rich in bilirubin. The hepatic parenchyma also contains hemosiderin and quite often shows necrosis.

Bone marrow: There may be an erythroblastic reaction.

Kidneys: Voluminous with brownish clots in the pelvis. Striae of the same color are seen in the medulla. Microscopically, hemosiderin can be seen in the epithelial cells, and besides this the tubules are often obstructed by casts of hematin. A little mononuclear infiltration and necrosis of the epithelium may also be present. There is a tendency to relate this tubular obstruction with the anuria; a further cause of this latter is undoubtedly the lowering of the arterial pressure. A similar renal syndrome of a tubulo-vascular nature with medullary congestion and cortical anemia has been reported in other pathologic conditions; crush injuries of limbs, incompatible transfusion, toxic hemoglobinuria, etc. The blood pigments can, in certain experimental conditions, cause renal insufficiency. Maegraeth and colleagues consider that in these cases renal anoxemia would occur following alteration of the blood or of the local capillaries or of the general circulation.

SYMPTOMATOLOGY

The patient is suddenly smitten by blackwater fever, sometimes when in apparently good health, or sometimes during an attack of malaria at any moment of its course or treatment. In any case the onset is abrupt: high *fever* resembling that of malaria because of its rigor and course. Sometimes, indeed, it is only a short attack lasting several hours and ending in sudation (benign cases), but at other times there is a remittent fever lasting for three to four days, and again at other times there are intermittent attacks spread over a week. The associated symptoms during the course of this pyrexia are variable, sometimes very serious; excitement, anxiety, vomiting, epigastric pain, painful congestion of the liver and spleen, hiccough. Consciousness is retained until almost the end. *Hemoglobinuria* with red or black urine of variable volume is as early a symptom as the fever. The urine may be normal in benign cases, increased in certain toxic cases, but more often tending toward oliguria or even anuria. The passage of pigment usually follows the curve of the fever and can also be intermittent with it.

Jaundice is the third main symptom. Always early (24 hours), it is often mild. In certain serious cases it becomes intense and can persist after the fever and the hemoglobinuria, greenish black urine (biliverdin) taking the place of the brownish red urine. Vomiting and bilious diarrhea are sometimes explained by the increase of bile production due to the massive hemolysis.

Anemia has already been mentioned, and can be intense. The blood count may fall in from one to three days to between 1 and 2 million red cells. The pulse may become weak and the blood pressure fall.

Clinical Course. This is rapid, either toward recovery (with only one attack) or at other times toward acute anemia, collapse, and exhaustion, or also toward anuria which, after being well tolerated at first, leads in several days to uremic coma and death.

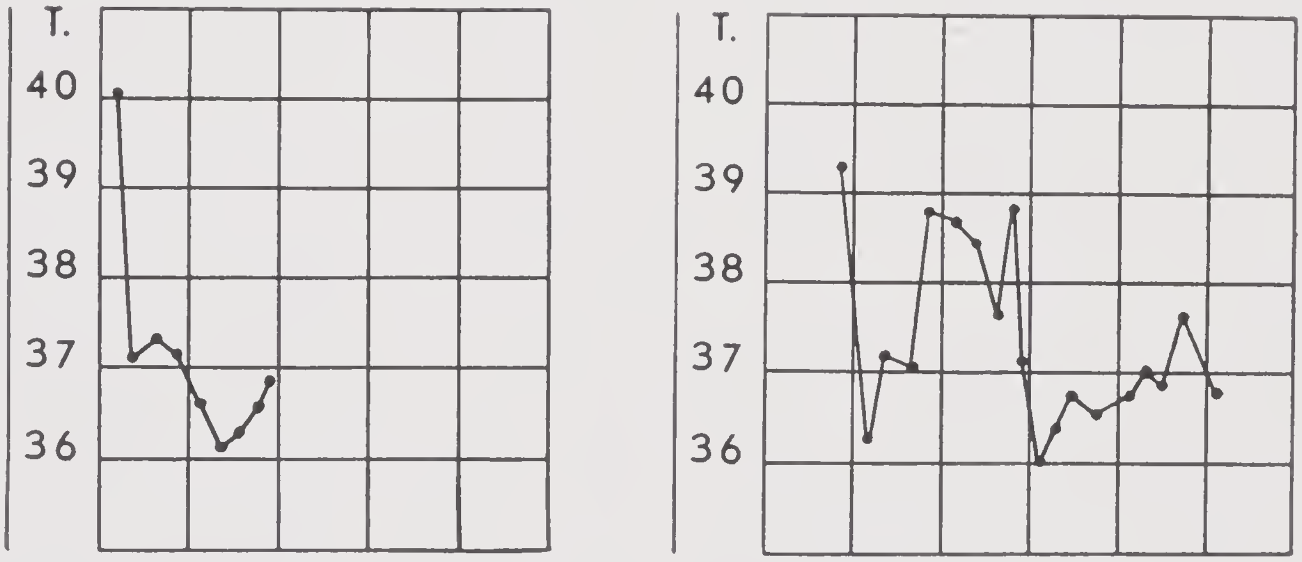

CHART 9. Two cases of benign hemoglobinuria in Europeans (Congo, Dr. Broden)

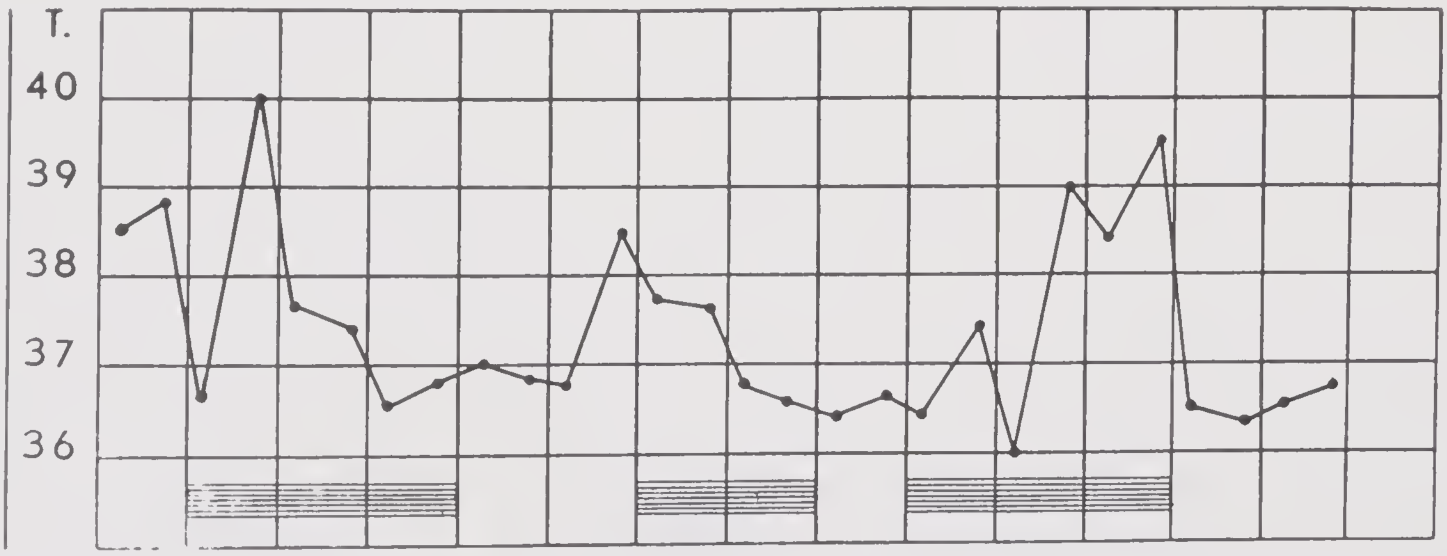

CHART 10. Hemoglobinuria during underlined days in a Negro boy 12 years old (Dr. Van Nitsen)

Clinical Types:

1. Mild and simple type: urinary output normal.
2. Fulminating type: abundant highly colored urine, vomiting, hiccough, intense anemia, collapse.
3. Oligo-anuric type: vomiting; at the end, uremic coma.
4. Prolonged and intermittent type.

There are incomplete forms which are more or less afebrile but with hemoglobinuria. Other still more atypical types are shown only by urobilin in the urine, and fever.

PROGNOSIS

This is still very reserved although there are many mild cases. (In a series of 10 successive cases seen by one of the authors in the Kasai there was no death, only 1 was very severe, another was serious and 8 were benign.) An average mortality of 15 per cent to 20 per cent is generally admitted. Furthermore, the tendency to relapses is considerable. Intense hemolysis, prolonged fever, hiccough and especially anuria are grave prognostic signs. Anuria is most often fatal. Superimposed nephritis is grave. The intermittent type is likewise serious. The convalescence is rapid in benign cases, but more monotonous and difficult in cases with gross hemolysis. Adequate treatment of the malaria improves the final prognosis.

DIAGNOSIS

The patient usually makes this himself on seeing his urine. It is easy for the doctor to determine that it is not a hematuria by examining the centrifugal deposit. More delicate, however, is the distinction between the various hemoglobinuric syndromes, among which may be mentioned:

1. Exogenous hemoglobinuria caused by poisons or infections.

(a) Blackwater fever is of this type, being caused by malaria or quinine and malaria. Repeated quinine hemoglobinuria would appear also to develop on a malarial foundation, appearing at each assimilation of the drug.

(b) Other infections: Scarlet fever, septicemias, especially that caused by *B. perfringens.*

(c) Various poisons: AsH_3, chlorates, sulfonamides, snake venoms.

The distinction between types (b) and (c) will have to be made from the history and the accompanying pathologic signs. With these poisons we must link the "Haffkrankheit" seen in the Bay of Königsberg, where a poison of industrial origin was found in the flesh of certain fish.

(d) Sensitization: Certain individuals react to the ingestion of seeds of *Vicia faba,*[*] or even to the inhalation of allergens produced by the flowers, by a severe illness comparable to blackwater fever. However, many people take this leguminous vegetable without harm. The condition, known as *favism*, while best known in Southern Italy, Greece, and Egypt, has also been observed in France. It had a mortality of 8 per cent in Sardinia. The Donath Landsteiner test is negative, as in blackwater fever. Diagnosis is possible only from the case history.

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[*] Var. major., Broad bean; var. minor., horsebean.

2. Endogenous hemoglobinuria.

(a) Paroxysmal hemoglobinuria, due to cold, appearing most often in syphilitics or in any case which gives a positive Bordet-Wassermann reaction. Its clinical appearance is strongly reminiscent of a benign attack of blackwater fever, but the history reveals repeated attacks which can be demonstrated at will experimentally by exposure to cold. In these patients the Donath Landsteiner test is positive (it is negative in blackwater fever), that is to say that the serum content of hemolysin fixed by cold (about zero degrees C.) on to the red corpuscles of the subject or of a normal person of the same group gives, in the presence of complement, a hemolysis of these corpuscles at 37 C.

(b) Hemoglobinuria after walking or exercise, attacking especially young males. A benign condition sufficiently identified by the circumstances of its appearance.

(c) Syndrome of Marchiafava-Micheli: This is a chronic affection producing severe anemia and with a poor prognosis. During the night, or more characteristically on waking, the patient suffers from a hemolysis, the urine containing blood pigments including some hemosiderin. It seems that the red cells of these patients are abnormally sensitive to a slight lowering of the blood pH, corresponding to the poorer nocturnal ventilation and acidosis. A pH of 7.0–7.2 causes hemolysis of corpuscles in vitro and this test has a real diagnostic value. Here also some methemalbumen is found among the plasma pigments. The hemoglobinemia is transitory (nocturnal), the hemosiderinuria is permanent.

(d) Finally there is a disease of horses which is seen on rare occasions in man. It is myoglobinuria, associated with muscular lesions which lead to paralysis. This disease is hereditary but has been occasionally seen in man. There are shooting pains in the legs, the muscles of which are hard and sensitive. The urine is red (myoglobin) and rich in creatin. The condition would appear to be related to progressive muscular distrophy. Sickle cell anemia could also produce hemoglobinuria.

Furthermore, the demonstration of hemoglobinuria is sufficient to distinguish blackwater fever from other febrile conditions associated with jaundice: yellow fever, Weil's disease where, in addition, the jaundice is later. Bilious remittent malaria also has a late jaundice but no hemoglobinuria.

TREATMENT

1. *Specific:* The question of the value of employing a specific antimalarial treatment is still under discussion. Few doubt that blackwater fever is of a malarial origin, but it is improbable that it is of a direct infective nature. French authors sometimes qualify it as "paramalarial," which recalls the celebrated distinction of Fournier between syphilis and parasyphilis. The parasites are rarely abundant and they disappear quickly during the course of the hemolytic process. Experience and statistics are in general in favor of abstaining from quinine and also plasmaquine. On the other hand, it would not appear to be necessary to abstain from atabrin. This should be given only if there are parasites present and then only in usual doses. On the other hand, as soon as the patient is convalescent, a complete antimalarial treatment must be administered cautiously, a watch being kept on the temperature and urine. It would be reasonable to start with atabrin at first in doses rising from 100 mg. to 300 mg. (1 week) later this can be followed by quinine (start with small doses). Paludrine might be preferable. Before atabrin was discovered, as soon as the urine was clear of pigment we gave 40–50 mg. of quinine three times a day progressively increasing till we reached 750–800 mg. a day, a dose which was continued for a long time. This was tolerated perfectly.

2. *General and Symptomatic:* The following are especially important:

(a) Absolute rest: avoid moving about or traveling as far as possible.

(b) Antihemolytic drugs: None have proved really valuable. Papaverine has been used extensively in the Congo and is innocuous (dose 40 mg.). Antivenom serum has been widely used but its action is not well established. Cholesterin and choline are no longer considered valuable. Vitamin K has been employed but its mechanism is not definitely understood. Burkett (1943) uses luminal sodium by injection.

(c) Cardiac stimulants: against collapse, camphor, caffeine, coramine, etc.

(d) Diuretics: against possible anuria, give abundant fluids, fruit juices, beverages, and champagne if the patient is weak. Enormous amounts of fluids have been advised but it would seem better to remain within physiologic limits, i.e., 2000–2500 cc. When vomiting occurs, rectal drip or injections of glucose saline are an important standby. If possible, chart the fluid intake and output.

(e) Alkalis: These have been advised on the theory that the precipitate from the tubules is acid hematin and that the alkalinization of the urine would avoid this precipitation. This view has been rejected by various authors (Maegraith). Fruit juice, sodium bicarbonate (500 mg. hourly), or "fruit-salt" (tartaric acid and sodium bicarbonate), saline bicarbonate injections (see under "Cholera") are useful to this end and are given until the urine is alkaline.

(f) To combat anemia: Blood transfusion has been used against acute anemia but it seems contraindicated in cases of anuria. It is valuable in fulminating cases with collapse, when the red cell count falls to 1,500,000. One should not be satisfied with determining the group of the patient but should verify the direct compatibility of the bloods. In convalescence: Good food, iron, liver extracts.

(g) To combat anuria: Hot compresses and cupping on the loins, intravenous hypertonic glucose injections (15 per cent, 50 cc.). Theobromine, caffeine. Warm, high colonic irrigations, irrigation of the renal pelvis. Parenteral fluids should be given cautiously.

Further various symptoms will require attention. Vomiting: ice, iced champagne, chloroform water. Excitement: small doses of morphia. Lastly, repatriation to temperate countries is desirable. It is very important to watch and control chronic malaria and anemia during convalescence.

PROPHYLAXIS

This is the same as for malaria in general. From the point of view of the practitioner it would appear preferable to treat chronic malaria and its exacerbations with atabrin, although this treatment has sometimes been followed by blackwater fever. The possible provocative role of Paludrine and Chloroquine are not known. An efficient treatment of malaria is of the greatest importance.

6. RELAPSING FEVER* (TICK FEVER)

Definition: Relapsing fever caused by blood spirochetes transmitted by arthropodes: lice (cosmopolitan forms *Sp. recurrentis*) or ticks (local forms *Sp. duttoni, etc.*).

HISTORY

The classic form of the disease has been known in Europe since the first half of the nineteenth century and has been described in particular by Murchison and Griesinger. In 1868, in Berlin, Obermeier discovered the spirochete in blood. Subsequently, various writers practiced inoculations on man and Metchnikoff performed a positive autoinoculation. Others, preceding Wagner V. Jauregg, made the first trials of fever therapy on cases of neurosyphilis (Rosenblum in Russia).

Though suspected by Mackie (1907) in India, the transmission by lice was established in North Africa (1910) by Sergent, and later Nicolle and their collaborators.

The African fever due to ticks has been known since Livingstone (1857). The spirochetal etiology of this fever was established by Ross and Milne (1904, Uganda) and especially by Dutton and Todd (1905, Belgian Congo) and Koch (East Africa). Later, a number of geographic varieties of tick fever were described, particularly the Spanish variety in 1920 (Sadi de Buen).

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* French: Fievres Recurrentes; German: Ruckfall Fieber.

GEOGRAPHIC DISTRIBUTION

Like its transmitter *Pediculus humanus vestimenti,* house relapsing fever is cosmopolitan; Eastern Europe, India, China, North Africa are the most widely known centers. Fairly recently the disease has spread to West Africa, the Anglo-Egyptian Sudan and coast of Kenya. It does not seem to have penetrated into Central Africa. It makes its appearance as an epidemic and frequently accompanies exanthematic typhus. From 1944 to 1946 great epidemics were met in North and East Africa and spread to the Middle East. Tick fevers are localized according to the vector: East and Central Africa (*Ornithodoros moubata*); Spain and Morocco (*O. erraticus*); America, from Venezuela to British Columbia, including the different States of the Southwest and West of the U.S.A. (various species, see below). They are endemic or sporadic.

In Africa *O. moubata* develops only in savanna country and the disease has not penetrated the vast forest zone of Central Africa.

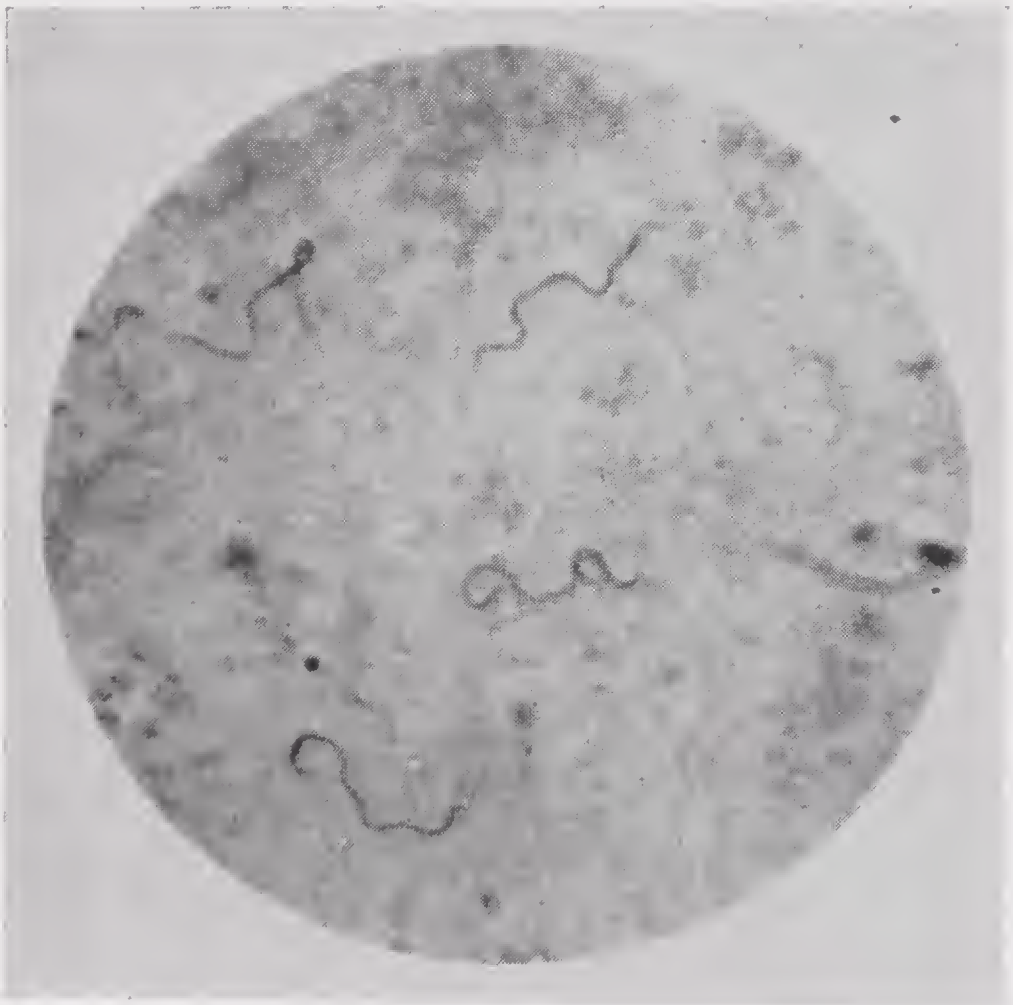

Fig. 24. Staining of Sp. duttoni

Spirocheta duttoni stained with Giemsa in a thick film preparation (coll. Tropical Institute, Antwerp)

ETIOLOGY

Spirochaeta or *Borrelia recurrentis,** a blood spirochete, 8 to 25 microns long and 0.2 wide, with from 3 to 10 spires, is the type species, possibly the only valid one, for the various relapsing fevers. Nevertheless, the name *Sp. recurrentis* is generally reserved for European relapsing fever transmitted by lice, while *Sp. duttoni* is the specific name retained for the Central African relapsing tick fever. The two species *recurrentis* and *duttoni* are, furthermore, different in susceptible animals. They do not possess cross-immunity, but this has also been noticed with different strains of *Sp. duttoni.* Numerous species have been described and although the validity of the classification is questionable, it has been maintained for the sake of convenience, because it refers to different regions and the transmission by local ticks.

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* Spirochaete is generally used in medical writings. Yet in protozoology the generic name Borrelia is more correct.

The following are the principal species of pathogenic "Borrelia" of man, their vectors, and their geographic distribution:

Causal Agent	*Vector*	*Locality*
Sp. recurrentis	Pediculus humanus	Europe, West Africa, and East Africa
Sp. berbera	Pediculus humanus	North Africa
Sp. carteri	Pediculus humanus	India
Sp. novyi	?	America
Sp. hispanica	O. marocanus O. erratious	Spain, Morocco
Sp. duttoni	O. moubata O. savignyi	Central Africa Abyssinia
Sp. persica	O. papillipes	Near and Middle East
Sp. turicatae	O. hermsi O. turicatae	California Texas
Sp. neotropicalis	O. venezuelensis O. turicatae	Central America and South America
Sp. venezuelense	O. talaje	

Other pathogenic "Borrelia" of domestic animals, including poultry, are known (*Borrelia gallinarum* and *Borrelia anserina* of hens and geese, transmitted by *Argas*). The blood Borrelias are easily cultivated on artificial media and on embryonated eggs. The pathogenic Borrelias of man which are transmitted by lice have as principal and perhaps exclusive reservoir of virus, man himself. Man is also often the main reservoir of virus for Borrelias transmitted by ticks (*Sp. duttoni*), but wild rodents may also act as such. Finally, for many kinds of relapsing tick fevers, the normal reservoir is to be found in wild animals (ground squirrels, chipmunks, *Eutamias sp.*, and tree squirrels, *Sciurus sp.*, in California, monkeys, marmosets, and opossums in South America), man only becoming infected should he happen to sleep near the burrows of rodents where the infected ticks exist or should he become directly contaminated by the blood of a rodent or other animal during its capture. Wild rodents may harbor *Sp. duttoni.*

According to Nicolle, relapsing fever is supposed to have its origin in an infection of wild rodents transmitted by ticks, and secondarily adapted to man through transmission by house ticks (*O. moubata*), and even more closely through transmission by lice. The parasites are easily found in thick drops of blood, taken during an attack of fever. They stain easily by the Romanowsky method and also by various basic stains.

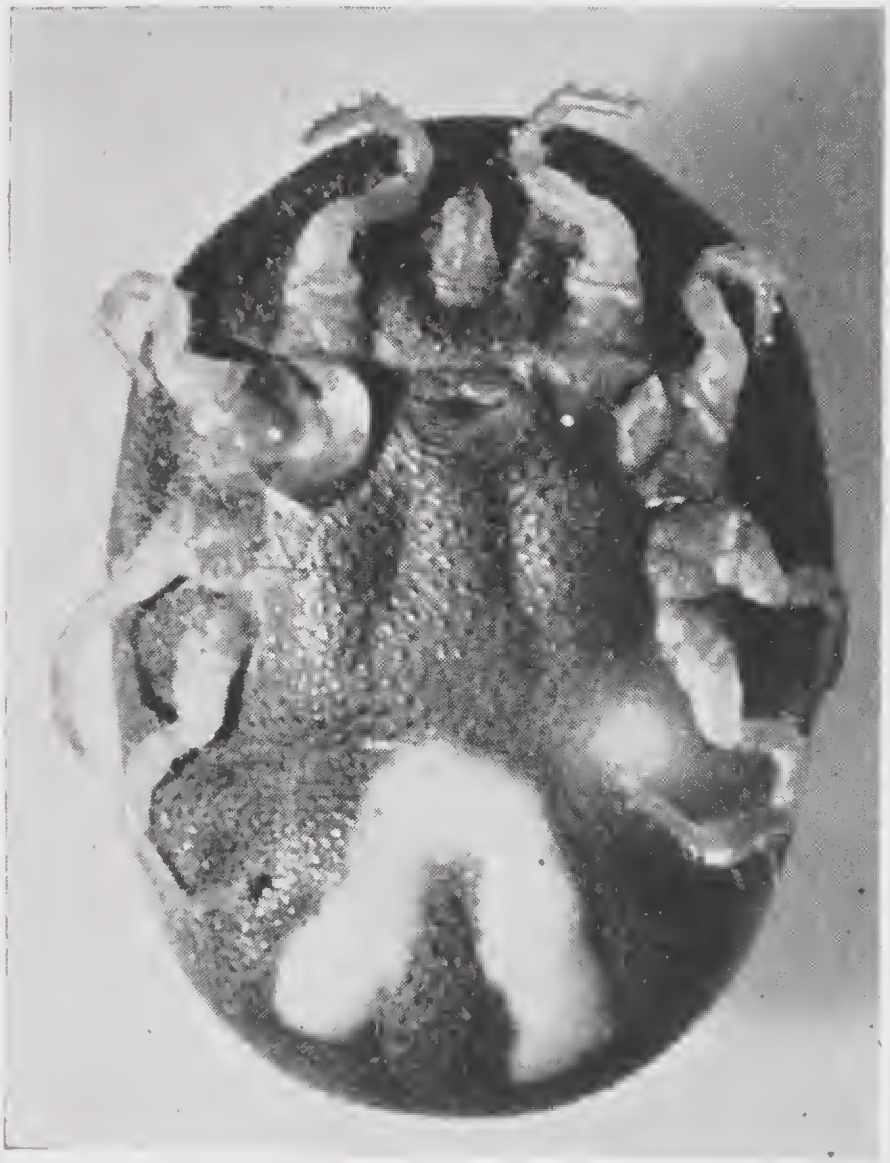

FIG. 25. ORNITHODOROS MOUBATA
Ventral side showing two drops of coxal fluid containing infecting spirochetes (phot. G. Boné, Tropical Institute, Antwerp)

The infection causes in man and in susceptible animals (rats, mice, monkeys) an immunity of fairly long continuance, probably due to a latent infection of the central nervous system. A small number of Borrelia would survive there, sheltered from antibodies by reason of the peculiar blood irrigation of the nervous tissue.

TRANSMISSION

Relapsing fever of Europe, India, China, and also of various countries of North Africa is transmitted by the body lice and head lice, *Pediculus* *humanus*. Four or five days after the infecting meal, the lice show numerous spirochetes in their coelomic fluid. From then on they remain infectious for two or three weeks. Transmission does not take place during the bite, but by crushing the louse and scratching the skin. This means contamination and not inoculation. Infection in the louse is not hereditary.

The transmission of parasites (*Sp. duttoni*) by ticks has been best studied with *O. moubata*. Infection is hereditary in these ticks and furthermore they can live and remain infectious for years without taking any meal. They hide during the day in crevices in the earth and in walls of habitations and native huts, preferably in dust or dry sand. They bite man only during the night (analogy with the Triatomes, vectors of *Trypanosoma cruzi*). The infected ticks seem to show spirochetes only in the coxal glands, regulating organs of ionic balance between ingested blood and the interior medium (Boné). During the meal, two thick drops of coxal fluid (see fig. 25) appear on the lower side of the tick, at the base of the first pair of legs. In this way the contamination of the skin and of the place of bite takes place. The salivary glands, the tubes of Malpighi, and the digestive tube do not seem to intervene in the transmission of *Sp. duttoni* by *O. moubata*. *O. hermsi,* however, transmits by bite (Wheeler). It seems that this mode of transmission might also be found with *Sp. duttoni* by *O. moubata* (Feng and Chung, 1938).

Experimentally at least, numerous arthropodes transmit these spirochetes: ticks, lice, but also *Cimex lectularius* and several Triatoma. It seems that human infection is possible by ingestion of spirochetes (this has easily been demonstrated experimentally). Transmission to the fetus may also be found in gravid animals and in woman through the placenta. The ocular conjunctival membrane seems a possible entry for infection. Laboratory contamination has been noted.

IMMUNITY

European physicians have drawn attention to the fact that re-infections can occur several months after a first infection. They can possibly be explained by the differences in the strains. Nevertheless, generally speaking, the infection leaves a true immunity in man and animals, but Bruynoghe and Dubois have shown that, with *Sp. duttoni*, this immunity is effective only for the strain in question. In other words the *Sp. duttoni* strains differ antigenically.

The results of these writers are more conclusive with regard to mice, yet it is possible that they may apply to men. It has also been ascertained that the spirochetes of a first attack are antigenically different from those of relapse, a fact also demonstrated with trypanosomes. The adaptation to the antibodies of the plasma is sufficient to modify the parasite ("serumfast" parasites) but it is doubtful whether this latter point is of any real practical importance. Nevertheless, it explains the several relapses which characterize the disease.

In countries where tick fever is endemic the adult natives are generally found to be immune. In mice this immunity is due to antibodies which appear late (35–40 days after inoculation) and which renders the blood sterile (noninfecting) and protective. Very frequently a cerebral residual infection persists which possibly intervenes in the maintenance of immunity, but which, nevertheless, does not seem to be a necessary cause. The parasites are probaby able to persist in other organs.

In man, the existence of antibodies has not given rise to any practical method of diagnosis.

It is worth mentioning that during the lytic crises which occur in man as well as in mouse, the blood is not completely free of parasites, as is shown by inoculation or culture. Isolated spirochetes, with a greater antibody resistance, circulate, and in multiplying and adapting themselves constitute the next wave of parasites. To consider the spleen as an organ of refuge between the attacks is here of no value. The spleen serves rather as a center for the lysis of the spirochetes altered during the attack.

PATHOLOGY

Fever is contemporary with the multiplication of the spirochetes in the blood. The pathology is that of acute infections: congestion, slight hemorrage. Very often there is jaundice and frequently additional lesions of an intercurrent disease (such as broncho-pneumonia). The spleen may show infarcti. The viscera show cellular degeneration (liver, kidneys myocardium). Various writers, and fairly recently Russel, have insisted on necrotic lesions of the Malpighian bodies of the spleen with demonstrable spirochetes. These lesions are sometimes visible to the naked eye, Malpighian bodies being more distinct and projecting than normally.

The well known neurotropism of the spirochete (whose presence in the brain has been ascertained both in man and in animals) manifests itself frequently by meningoencephalitis with reaction in the cerebrospinal fluid.

Recently Taft and Pike (1945) found *Sp. turicatae* in the derm of subjects having an erythema polymorphum in the course of the infection (even in absence of fever).

SYMPTOMATOLOGY

We will not describe separately the lice fever and the African tick fevers, from which other tick fevers, though often of a milder character, differ very slightly.

Incubation generally takes from eight to ten days.

Invasion is sudden with very high fever, severe headache, and various pains. During the course of the first febrile attacks the symptoms associated with them are very clearly indicated and they often diminish during later attacks: bilious vomiting, jaundice, epigastric pains, spleen and liver congested and sensitive. Concerning the nervous system, one notes agitation, delirium, depression. The attacks end in a crisis.

The characteristic of the illness resides in the evolution of the fever. In the cosmopolitan form the attacks are fairly long (which fact, with the already quoted nervous signs, justifies the name "relapsing typhus," which is sometimes used) and they are not numerous (generally two to three, sometimes a single one). In African tick fever the attacks are much shorter (the first and the second: 3 to 4 days, the following ones 1 to 2 days) and more numerous (averaging 5 to 6 and up to 8 and 11 days). In any case, the apyretic intervals vary in length (a few days) and are asymptomatic.

Complications are fairly numerous and often intervene in the mortality; this is especially true of pathologic conditions of the lungs. Nephritis or hepato-nephritis is sometimes noticed. A slight feverish albuminuria is frequent. Epistaxis, an exanthema sometimes petechial, and labial herpes are encountered. The spirochetal infection fairly often determines ocular manifestations: iritis, choroiditis, and nervous states: deafness, facial paralysis, etc.

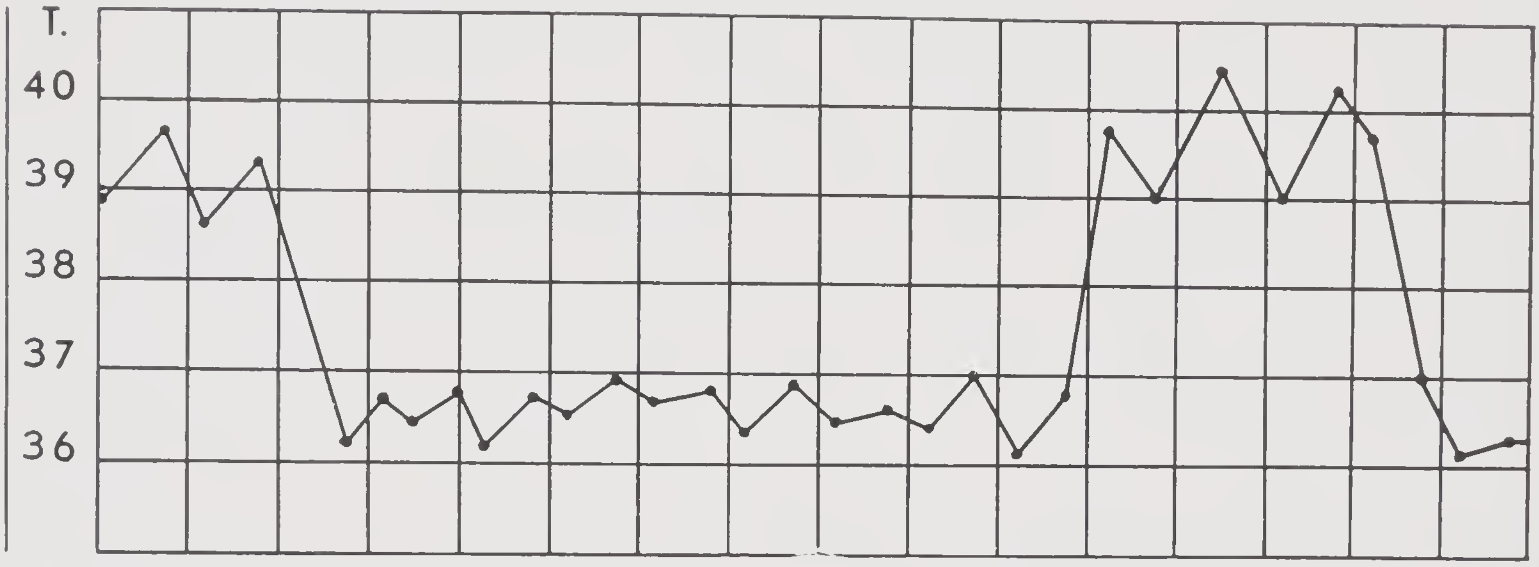

Chart 11. Cosmopolitan relapsing fever. Part of the curve (semischematic)

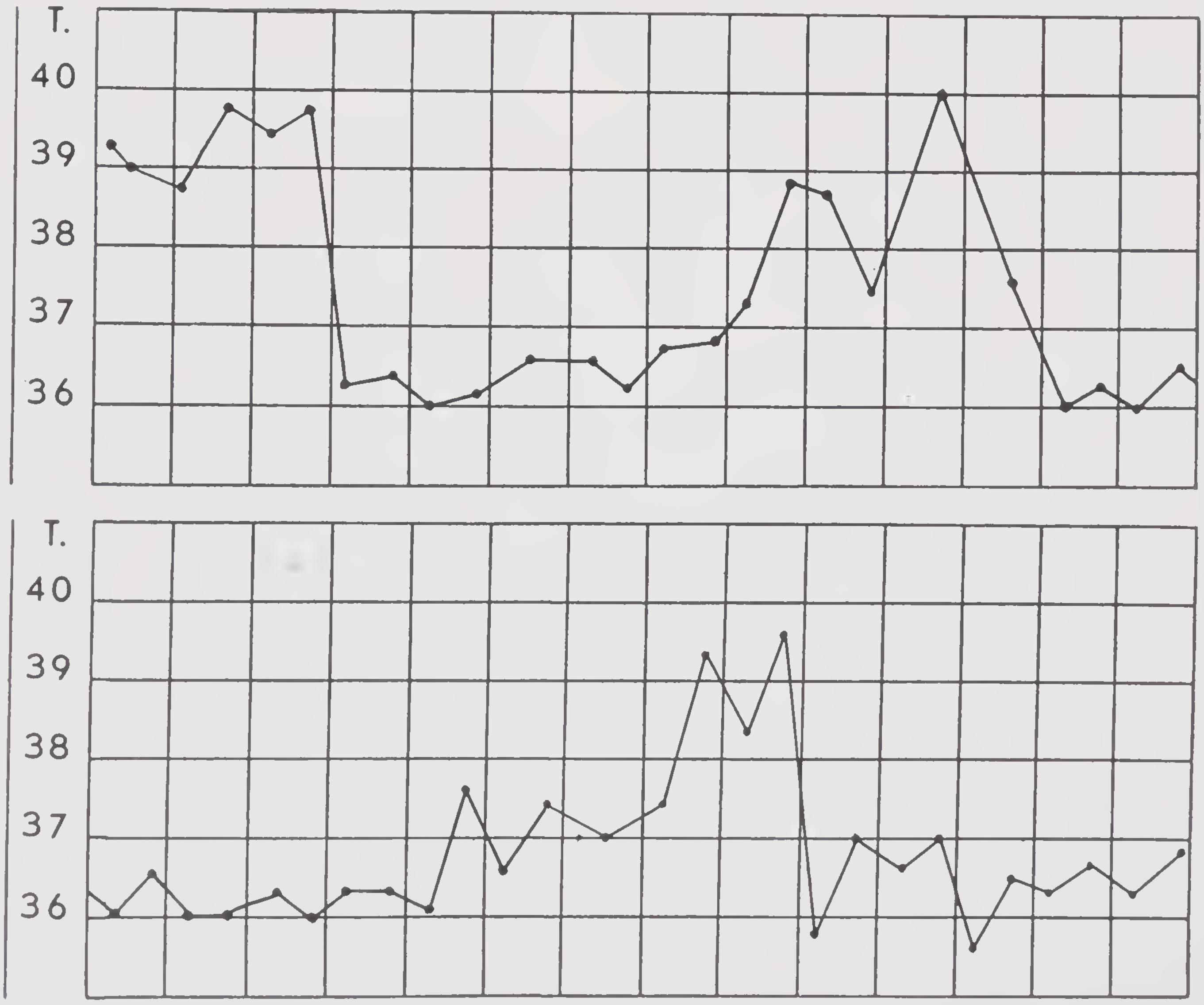

Chart 12. Part of the curve of tick relapsing fever (semischematic)

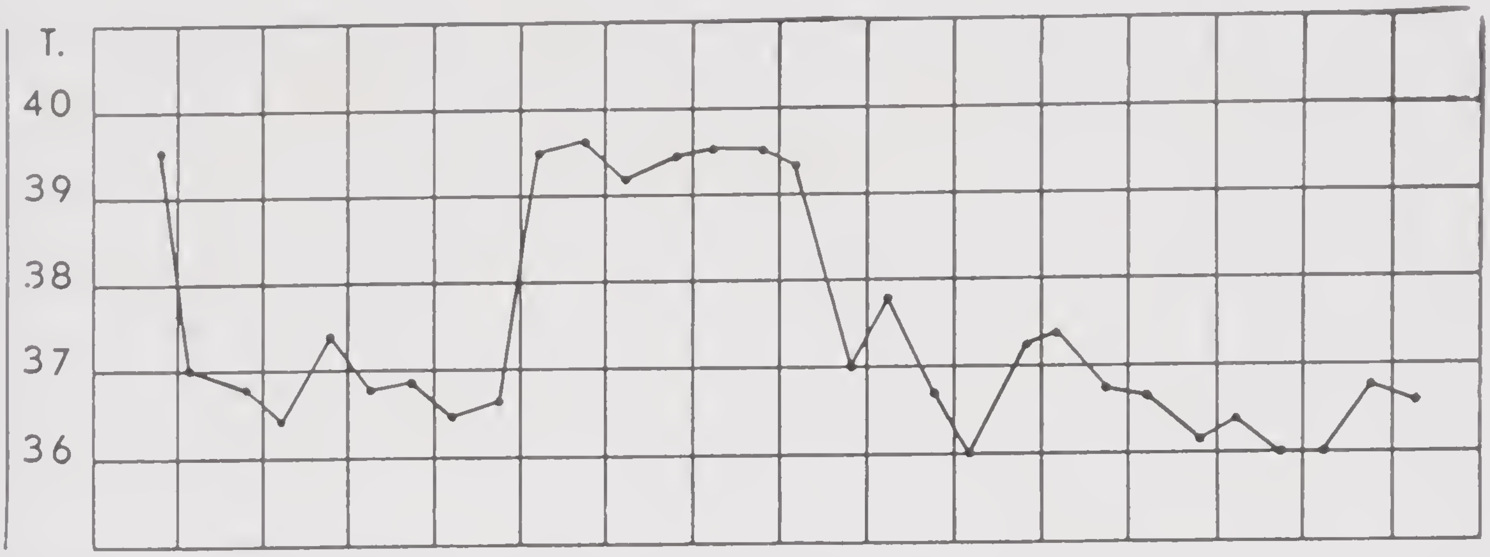

CHART 13. Tick relapsing fever from Katanga, very much of the European type (Dr. Mouchet)

Clinically, attention has been drawn to a meningitic condition; the intense cephalalgia is significant.

From 1910 on, Rodhain and his collaborators had shown the frequency of a lymphocytic reaction in the spinal fluid with slight general disturbances. These facts have been confirmed elsewhere. Various writers have been able to infect animals with the spinal fluid and have observed parasites in it. All this is in agreement with the neurotropism observed in mice, etc. (Buschke and Kro). Benhamou and colleagues (1946) draw attention to the presence in Algeria of bradycardia, especially during the apyretic intervals, as well as of cardiovascular adynamia with low tension. Less frequently have signs of acute articular rheumatism and complete collapsus been noted.

The bilious typhoid fever of Griesinger, formerly observed in the Mediterranean area, is an infectious icterus of which the retrospective diagnosis is not clear and may vary: severe relapsing fever, leptospirosis, etc.

PROGNOSIS

The prognosis is generally favorable quoad vitam. The average mortality is 5 per cent. Nevertheless, epidemics considerably varying in gravity have been noted. In certain instances (Europe, India, etc.) the gravity could be ascribed to social conditions (war, famine, etc.). In West Africa, however, and in the Sudan, the death rate has generally been high (25 per cent) in spite of fairly good living conditions for the populations referred to. During the crisis a collapsus is to be feared.

Ocular complications are functionally serious.

It will be remembered that Dutton succumbed to the disease in the Congo, but according to Dr. Heilberg who accompanied him, his health was not in perfect condition when he left Europe and that seems to account for the fatal termination of his malady (personal communication).

The susceptibility of Negroes to pneumopathias possibly explains the gravity of certain epidemics.

DIAGNOSIS

Clinical diagnosis is easy only with a classic temperature curve, and this information is not available in the early stages of the disease. At the beginning, the illness might easily be taken for malaria, dengue, yellow fever, and even exanthematic typhus; in fact, quite a number of sudden pyrexias. The intensity of the headache points to relapsing fever.

Actually the modern physician who, at the onset of any kind of fever, neglects the research of parasites in the blood commits a professional error and loses the opportunity for diagnosis, which, because of treatment, may never occur again. A simple blood smear may show parasites, a thick drop always being more certain.* The dark field condenser which is so useful in a laboratory is less practical for the physician.

It is important to remember that, contary to what happens in malaria, examination in relapsing fever is positive only during the febrile periods. During the apyretic intervals, however, hemoculture on special medium or inoculation of susceptible animals will show the existence of latent infections.† The number of parasites varies greatly. During the relapses they may be quite scarce. The blood shows leukocytosis.

Serologic methods have yet to achieve definite importance. Lumbar puncture provides useful information which must be interpreted with prudence while considering the other causes of meningitic reaction (sleeping sickness, syphilis, etc.). The reactions of Bordet-Wassermann and Kahn are negative. The benzoin reaction might be positive, in the syphilitic zone.

TREATMENT

After the discovery of 606 (arsphenamine), Iversen in Russia pointed out the activity of the product against *Sp. recurrentis*, and Rodhain and colleagues in the Belgian Congo extended this finding to *Sp. duttoni*. These writers made use of very large doses, i.e., 10 mg. of arsphenamine per Kg. of body weight. The parasites disappear in four to six hours and the fever in twenty-four hours.

At present, neoarsphenamine is used in doses varying according to the writers. For a dose of about 10 mg. per Kg. of body weight, the effect is generally powerful. In practice, 600 mg. for the adult, repeating the dose after four days (three times in all) has proved to be very satisfactory at the beginning of the infection, except for certain strains which are not very susceptible to arsenic (this applies especially to *Sp. duttoni*). When applied after several attacks the result is often less favorable, the nervous system probably being already invaded.

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* Both methods should always be coupled.

† One can inject 2 to 3 cc. of blood into a monkey or divide 2 cc. among four mice (incubation 2 to 6 days).

It is advisable not to use the product during apyretic intervals, nor while the patient is at crisis and a collapsus possible.

Other writers give increasing doses, that is: 300–400–600–600 mg. for the adult, at intervals of two, three, then four days. This prudence is justified if the general condition of the patient seems very impaired. Too strong a treatment sometimes results in rather severe reaction, not to mention the characteristic toxicity of the arsenobenzenes. Toward the end of the series of attacks, it seems necessary that treatment by trivalent arsenical give way to the following, which appear to be "neurotropic":*

1. *Pentavalent Arsenicals:* Stovarsol per os to the total dose of 50 mg. per Kg. body weight in three days, or intravenously (Sodium Stovarsol); also Sodium Orsanin, 2 to 4 times, 20 mg. per Kg., at intervals of five days (Boiron 1947). The effect of these products is often imperfect (strain only slightly arsenosensitive).
2. *Gold:* Solganal, Solganal B, Solganal Oleosum, and Oleochrysobiose have proved experimentally to possess a therapeutic action superior to that of arsenic, even on cerebral infections. This has been less well established in the human. Gold seems principally indicated in the nervous period: 400 mg. intramuscularly of Oleosolganal and repeat.
3. *Penicillin:* This antibiotic represents an acquisition of importance. It is particularly suitable in cases of jaundice and weak subjects. About 500,000 units should be given. The spirochetes disappear within twenty-four to forty-eight hours.

PROPHYLAXIS

In lice relapsing fevers, prophylaxis is limited to the destruction of the lice. The dusting with 10 per cent DDT in talcum rapidly kills all the adult lice and the effect of a single application is maintained long enough to kill the lice as soon as the nits are hatched (see exanthematic typhus). In the case of relapsing fever due to house ticks, the individual prophylaxis is easy. One need only sleep in a tent far from habitations or in a house with cemented floor. Sprinkling the floor with water or maintaining a light at night is a protection in suspected houses. If the legs of the bed are placed in containers full of any kind of liquid or disinfectant, the protection is complete. The best way to realize social prophylaxis would be to burn down all contaminated habitations and to forbid all constructions made of earth and straw, using bricks and cement instead.

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* The trivalent arsenicals of the arsine oxide type (Mapharsene, etc.) have been less in use, but are active (40 to 60 mg.) intravenously.

In cases of relapsing fever due to rodent ticks it is imperative to avoid sleeping near burrows which are suspect.

7. RICKETTSIAL DISEASES*

General Definition: It is permissible to group a certain number of diseases characterized by a sudden onset, a morbilliform or petechial eruption, continuous fever lasting from ten to twenty days and fairly frequently showing prostration. All of them are due to Rickettsias and are transmitted by Arthropods.

Several of these diseases belong rather to temperate countries, but their inclusion in handbooks on tropical medicine is classic and justified by their relationship.

GENERAL ETIOLOGY

The Rickettsias constitute a group of micro-organisms of undetermined position in the classification. They are common in Arthropods and their characteristic habitat is intracellular. Cocci or bacilliform, the Rickettsias are mostly present in the cytoplasm of the cells, sometimes in the nucleus (Rocky Mountain fever), at other times they are isolated on the smears after the rupture of the cells. They are difficult to stain with aniline colors and by the Romanowsky method. The Machiavello coloring (see Appendix C) stains them red. Only Rickettsias of Q fever pass through filters (Berkefeld N.). The Rickettsias, like the viruses, can be cultivated only in the presence of living cells or on chick embryos. Very fragile, they can be kept alive only by desiccation and maintaining at low temperature. The laboratory tests permit the separation of Rickettsial diseases:

1. By the behavior of experimental animals, especially male guinea pigs of 400 to 500 Gm., injected into the peritoneal cavity with 5 cc. maximum of human blood taken at the onset of the infection. The normal maximum temperature of the guinea pig is 39.5 C. The temperature is taken rectally, the thermometer pushed to a depth of at least 5 centimeters.
2. By the determination of the transmitting Arthropode.
3. By the agglutination test of Weil Felix (Proteus X).
4. By the specific agglutination and the complement fixation tests of Rickettsias obtained by culture.

TRANSMISSION

Several groups of Rickettsial diseases have been defined by their immunologic properties and by their mode of transmission by special Arthropods:

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* French: Rickettsioses; German: Rickettsiosen.

1. *The typhus group.*

Exanthematic, epidemic, historical or human typhus, due to *Rickettsia prowazeki*, transmitted by *Pediculus humanus* (*corporis*) and *Pediculus humanus* (*capitis*); exanthematic, endemic, or murine typhus, due to *R. mooseri*, transmitted principally by *Xenopsylla cheopis* and *Ceratophyllus fasciatus;* Brill's disease, apparently a mild form of human typhus. Belonging to the same group are: the Mexican Tabardillo, the nautical fever of Toulon, the typhus of Manchuria and the urban typhus of Malaya.

2. *The group of Rocky Mountain spotted fever.*

Rocky Mountain spotted fever, due to *R. ricketts*i, transmitted by *Dermacentor andersoni*, *D. variabilis* and *Amblyomma americanum;* Typhus of Sao Paulo (Brazilian spotted fever) and Tobia fever of Colombia, due to *R. rickettsi* and transmitted by *Amblyomma cajennense.*

Fievre boutonneuse and Kenya typhus, due to *R. rickettsi subsp. conori*, transmitted by *Rhipicephalus sanguineus;* South African tick bite fever, due to *R. rickettsi subsp. pyperi*, transmitted by *Haemaphysalis laechi* and *Amblyomma hebraeum;* Tick typhus of Siberia, transmitted by *Dermacentor nuttali;* Bullis fever transmitted by *Amblyomma americanum;* Rickettsialpox transmitted by *Allodermanyssus sanguineus.*

3. *Group of Tsutsugamushi.*

Tsutsugamushi, due to *R. orientalis*, transmitted by *Trombicula akamushi* and *T. deliensis*. Deriving from the same etiology are the rural typhus of Malaya, the Myte Koorts of Sumatra, the scrub typhus, and the Queensland costal fever.

4. *Group of Q fever; clinically distinct from the former.*

Q fever from Australia, due to *R. burneti* and transmitted by *Haemaphysalis humerosa;* American Q fever, due to *R. burneti subsp. diaporica*, transmitted by *Dermacentor andersoni* and *Amblyomma americanum;* European Q fever, perhaps directly transmitted.

5. *Group distinct from pathological point of view and of which the Rickettsial etiology is dubious.*

Trench fever, and Febris Volhynica; trachoma, venereal lymphogranuloma and psittacosis, previously reported by certain writers as Rickettsial diseases, are actually considered as virus diseases.

(A) *Epidemic Typhus Fever**

Definition: Endemo-epidemic disease caused by *Rickettsia prowazeki*, transmitted by *Pediculus humanus vestimenti* and characterized by fever, an exanthema generally petechial and a state of complete prostration (typhus state).

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* French: Typhus Exanthematique; German: Flecktyphus.

HISTORY

Epidemic typhus may possibly have been mentioned by Saint Cyprian, Bishop of Carthage (250 A.D.). The disease was individualized in the Renaissance and was observed at the siege of Granada in 1489 and during the siege of Naples in 1523. Fracastor described the condition in 1546.

During the sixteenth and seventeenth centuries the disease raged during the wars against the Turks (Hungarian disease), and in the Thirty Years War (1618–1648). It was probably introduced into America by the conquistadores and established itself in Mexico, Peru, Chile, etc. It prevailed during the European wars of the nineteenth century (Napoleonic campaigns between 1800 and 1815, Crimean War of 1853). There were practically no signs of typhus in the American Civil War (1861–1865). More recently during the First World War, terrible epidemics ravaged Serbia, Roumania, Poland, and Russia. In the latter country, from 1915 to 1925, 25,000,000 cases were reported, of which 3,000,000 died. In Western Europe, epidemic typhus had practically vanished during the last century and did not reappear during the First World War, not even in the armies where pediculosis was frequent.

The Second World War (1939–1945) saw a revival of typhus epidemics (North Africa in 1941, Iran in 1943, Naples in 1943) and a few cases were observed in Western Europe (isolated cases in Belgium). Typhus flared up also in Spain during and after the Civil War of 1935.

Though the general history of typhus is a long established one, its scientific history is fairly recent. The transmission by lice was established by Nicolle in 1909 (Tunisia).

The name *Rickettsia prowazeki* recalls the names of two scientists who succumbed to the disease: Ricketts in Mexico (1911) and Prowazek in Prussia (1916).

GEOGRAPHIC DISTRIBUTION

Eastern Europe, Minor and Central Asia, India, and North China are centers of outstanding importance due to the density of their populations and the frequency of wars. North and South Africa and in a lesser degree certain districts of high elevation in Central Africa (Uganda-Urundi) must also be quoted. In the Americas, Mexico, Peru, and Chile are the most important centers. Typhus is a disease of cold countries, or, in any case, of high altitudes. The cold is responsible for the crowding of the people and their use of dirty clothing.

ETIOLOGY

Rickettsia prowazeki is the etiologic agent of which the animal reservoir is vague, man being the principal source of infection.

An inoculted guinea pig, after an incubation period of 6–12 days (temperature from 38.5 to 39.5 C.), generally shows a rise on the ninth day, then a fall on the tenth, remaining stationary at 40 to 41 C. for five or six days with a two- to three-day lysis. The disease provides the animal with a distinct immunity for the diseases of the first group. The immunity test is indispensable for the identification of the disease in the guinea pig.

TRANSMISSION

Parasites are transmitted from man to man by the excrements of body lice, *Pediculus humanus corporis* and *P. humanus* (*capitis*), principally by scratching of the skin, crushing the lice, and injuring the epiderm.

PATHOLOGY

The Rickettsias are intracellular parasites, particularly of the vascular endothelial cells. The parasitic result is injury to the capillaries and small vessels with swelling of the endothelium, sometimes necrosis and thrombosis. These vascular alterations are surrounded by a reactional nodule (typhus nodule) sometimes more especially infiltrating (lymphocytes, histocytes, plasmocytes), at other times more proliferous (neuroglia). The association of small vessel lesions with typhus nodule can be considered as pathognomonic. The finding of Rickettsias in the endothelial cells (a rather difficult task) brings definite proof. The nodules, sometimes called Fraenkel's nodules, are seen in the skin (exanthema), the muscles, the myocard, and more especially in the central nervous system (cortex, cerebral trunk, marrow).

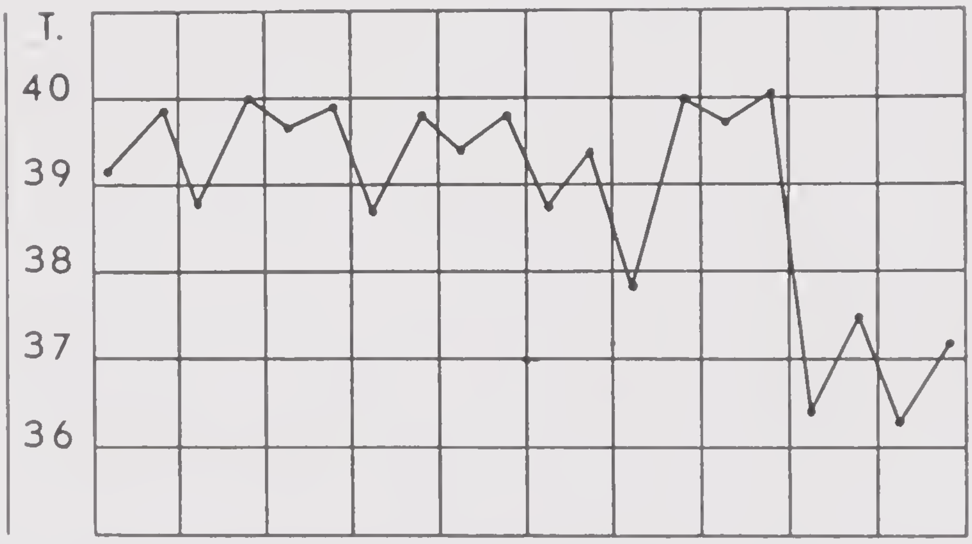

CHART 14. Epidemic typhus from Urundi (Drs. Pergher and Casier)

According to Golden (1945) relation between vascular lesions and inflammatory foci is to be met with only on the surface of the nervous tissue, the skin, and the testicles. Degenerative or inflammatory alterations (mononuclear cells) have been observed in different organs; liver, myocard, testicles, kidney, and spleen. The thickening of the walls of the lung aveoli is fairly common.

The macroscopic lesions reveal no data of special importance except what the clinic has already shown: a remaining exanthema, thromboarteritis, pulmonary complications, voluminous spleen, swollen testicles.

SYMPTOMATOLOGY

The incubation period is on an average of ten to twelve days, and usually symptomless. The onset is very sudden: high fever, shivering, cephalalgia, and general malaise.

The fever reaches 40 C. from the third to the fifth day and persists uninterruptedly for ten to fifteen days, after which the temperature rapidly falls.

The exanthema appears from the fourth to the sixth day, first of all on the sides of the trunk and the inner surface of the arms, and spreads to the whole body except the neck and face. The palms of the hands are rarely attacked, and even less so the soles of the feet. The eruption is first roseoliform, becoming petechial after two or three days. It is barely noticeable, if at all, in colored people. Extensive escharotic ecchymoses are also seen.

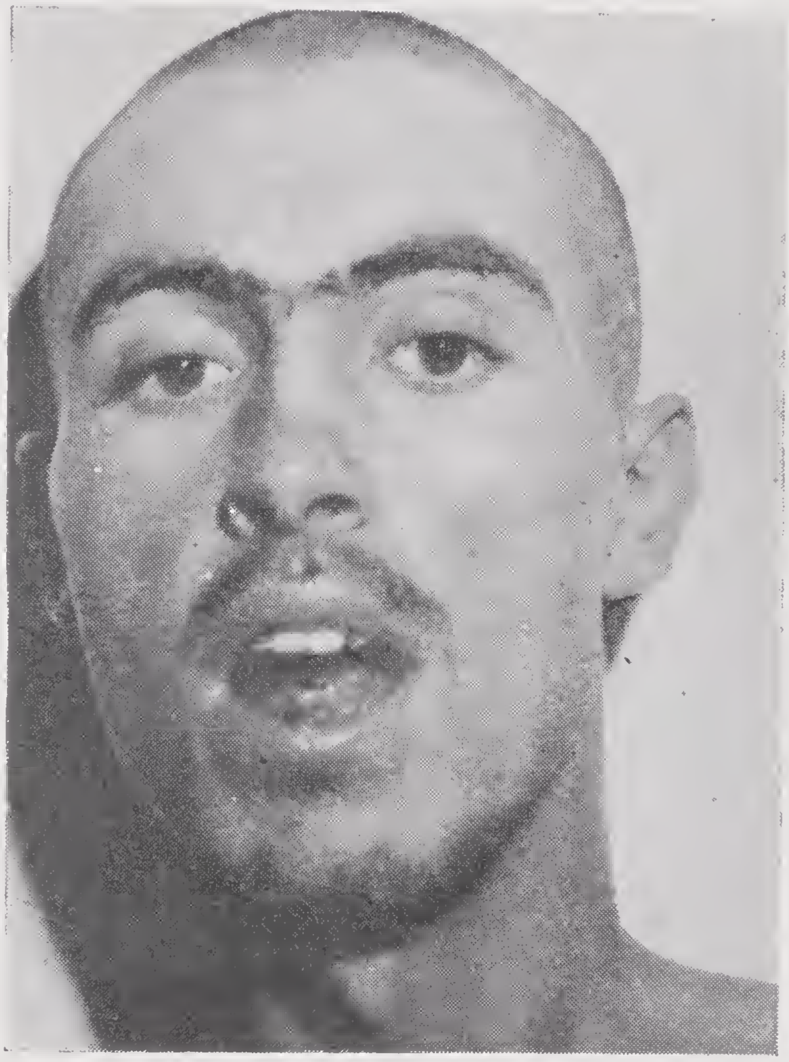

FIG. 26. EPIDEMIC TYPHUS
Note the stupor and the tongue hemorrhages (Army Institute of Pathology, Neg. No. C4345, Washington 25, D. C.)

The nervous system is seriously affected: intense headache, rachialgia, delirium, then progressively prostration, drowsiness, disturbed by agitation. This typhic state appears after three to four days and reaches its maximum about the eighth or tenth day. It sometimes continues until a state of coma.

The circulatory apparatus shows very notable symptoms: myocarditis with a weak and quick pulse, slight anomalies of the electrocardiogram, low arterial tension, dyspnea and cyanosis. Death may be due to asystolia, even after the fall of the fever. The circulatory troubles seem to be due to vasomotor mechanisms. The respiratory apparatus reveals "toxic" dyspnea at the start, then hypostatic congestion and, fairly often, foci of broncho-pneumonia.

Regarding the digestive tract, constipation is noted.

Fairly frequently occurring symptoms which have been quoted are: congestion of the face, dry and fuliginous tongue and mouth, rare and slightly albuminous urine (positive diazo reaction), clinical and humoral reaction of the meninges. Certain patients can stick their tongue out only with great difficulty (see fig. 27).

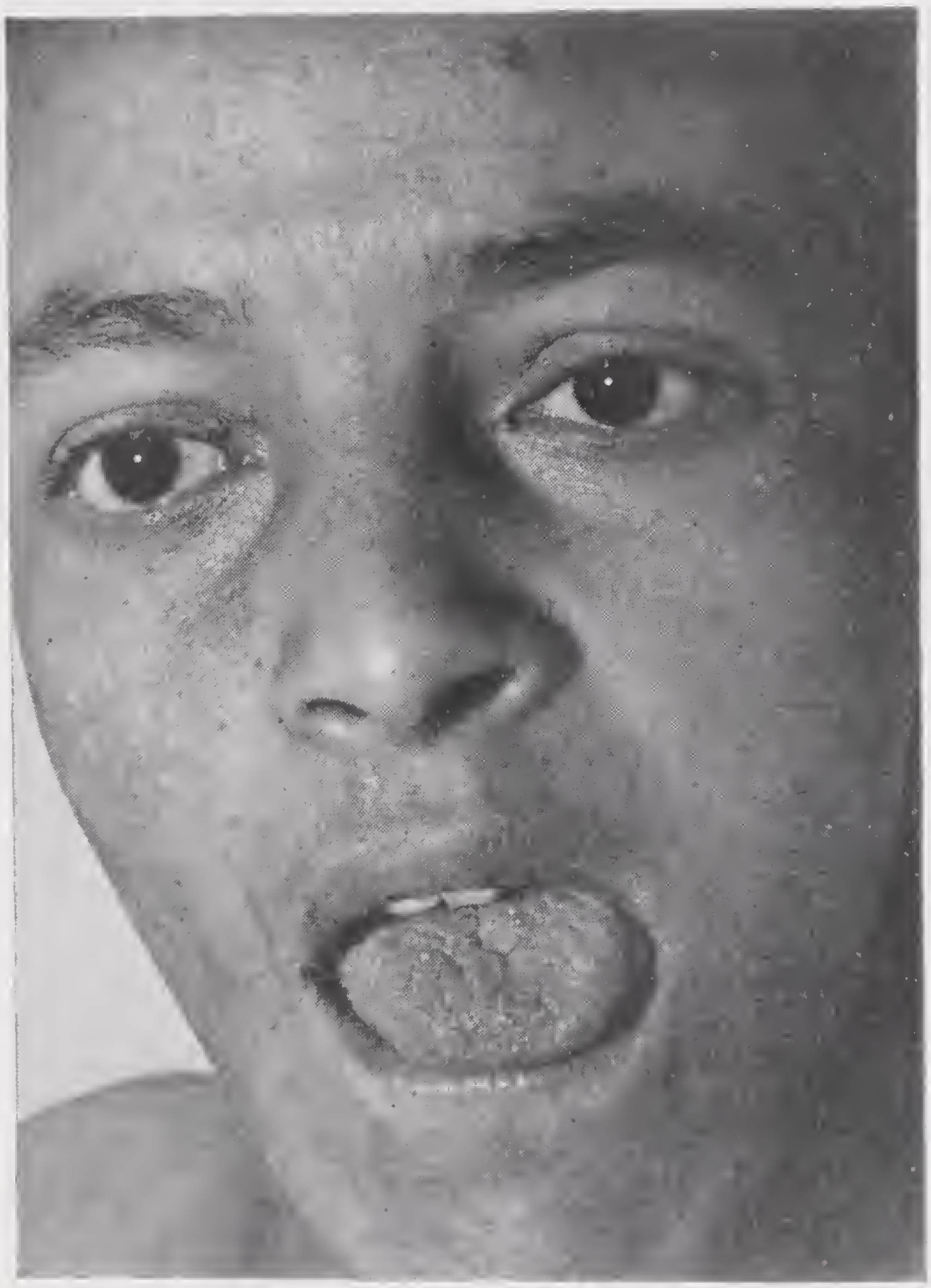

FIG. 27. EXANTHEMATIC TYPHUS
Army Institute of Pathology, Neg. No. C4346, Washington 25, D. C.

Complications: These are numerous: suppurating parotiditis, otitis, pneumonia, purulent pleurisy, edema of the glottis, fever, noma. Gangrene of the toes or feet is especially found in cold countries (quoted by St. Cyprian).

PROGNOSIS

The prognosis in typhus is severe, particularly in older people. In children the evolution is more discrete and favorable. The average mortality is 20 per cent. Death occurs either by aggravation of the nervous state (coma) or by circulatory insufficiency.

DIAGNOSIS

The triad of fever, petechial exanthema, and typhus state is fairly characteristic.

Typhoid fever develops more slowly than certain other febrile maladies. Relapsing fever will be easily recognized microscopically, influenza possesses less nervous symptoms and more respiratory complications and its propagation is more sudden.

The laboratory offers two valuable diagnostic methods. The first is inoculation of the guinea pig as mentioned in the etiology. The second is the study of the seric properties of the patients.

1. Weil-Felix reaction: In 1916 these authors isolated from the urine and blood of typhus cases strains of *Proteus bacilli* which were agglutinated by the serum of the patients. Strain X19 has proved to be the most sensitive, and its variety O (incapable of extension on gelose). The mechanism of the reaction is unknown. No relationship has been found between Proteus and Rickettsia. These germs probably have antigens in common. The reaction is empirically valid: it appears from the fourth to the sixth day, remains at its maximum from the eighth to the twentieth day and decreases rapidly to nil five or six months after the illness.

Agglutination up to 1/160 is considered without significance. It can reach 1/20,000 and more. The technic is the same as for Widal's test. Bridges advises the use of a suspension of microbes killed by alcohol (destruction of the antigen H). Then, after eliminating the alcohol, a suspension is made in formolized physiologic water. This method has the advantage of palliating the possible mutation from O to H. It gives lower agglutination rates than the living antigen. Plotz utilized strains of which the immobility had been verified. The rise of the agglutination rate is the most characteristic. This statement applies to all agglutinations, and all practioners should, therefore, take the blood as soon as possible. A negative result should be rationally interpreted and the blood re-examined in due time.

2. Agglutination or complement deviation of Rickettsias: Weigl's reaction consists in the agglutination of Rickettsias from lice (less practical). It is also possible to carry out the agglutination or the complement deviation tests with Rickettsias obtained from cultures. Contrary to the reaction of Weil-Felix, the above mentioned tests can differentiate epidemic typhus from Rocky Mountain spotted fever and even from murine typhus. The same differentiation is possible in the guinea pig (Plotz).

It should be observed that the serums may contain anti-Eberthella agglutins, sometimes at high titer, especially in people who have been vaccinated against typhoid fever.

TREATMENT

Injections of serum from convalescent cases have been used in epidemic typhus and also in other Rickettsial diseases. This practice, when utilized at an early stage, seems favorable to several writers. During the epidemic in Urundi in 1934, results were hardly appreciable.

More recently, p-aminobenzoic acid used during the course of the first week has been considered advantageous by various observers. This substance is given by mouth together with sodium bicarbonate (10 cc. of a 5 per cent solution per gram of acid). The first dosis is 8 Gm. followed by 3 Gm. every two hours. A plasmatic concentration of 30 to 60 mg. per 100 cc. is the goal. The tolerance is satisfactory. Total doses from 200 to 500 Gm. have been given. Naturally, in the event of infectious complications, such as pneumonias, etc., one would turn to penicillin and not to sulfonamides, of which p-aminobenzoic acid is an antagonist.

In addition, the symptomatic treatment of grave infections is indispensable.

PROPHYLAXIS

Epidemic typhus is almost exclusively transmitted by lice. Yet contamination by inhaling is possible. Accidental laboratory infections have occurred through small drops laden with Rickettsias during the various manipulations of infected tissues. The personnel of delousing stations is also exposed to infection by inhalation of dust infected with dry excrements of lice.

When a typhus epidemic begins to spread, every house in the region must be searched for cases. Patients must be sent to typhus hospitals, bathed, deloused, and their clothes disinfected. Then the disinfection of the houses where cases have been found must be effected, quarantine stations established with facilities for delousing, baths, and disinfection. All traveling in the region must be limited, especially by trains which must also be disinfected.

A particularly efficient method of destroying lice consists in the powdering of the whole population with 10 per cent DDT in talcum or pyrophyllite. The DDT kills the lice almost immediately by contact. The eggs are not affected, but the action of the DDT is so durable that it lasts until the hatching of the young lice, so that a single powdering suffices to make sure of a complete delousing. Individual protection has also been assured by using only such underwear, stockings and other clothing which have been soaked in an emulsion of 2 per cent DDT and then dried. Even after a subsequent washing, the insecticide is still present in a killing proportion. The use of this very active product has pushed all the former methods like mechanical delousing, bath, shaving, different ointments, into the background. All necessary details are to be found in treatises on dermatology and hygiene.

Vaccination against epidemic typhus is not an absolute safeguard against infection, but it attenuates the disease to a great extent. The respective value of the different methods still remains a much discussed subject. We abstain from stating a definite opinion, but must point out the risk involved in the use of living Rickettsias for a vaccination, in spite of the fact that these Rickettsias belong to the less virulent murine strain.

Living Vaccines: (1) Blanc uses murine virus from Morocco, living but attenuated by bile. Three million people have been vaccinated in this way in North Africa (1941–1943). (2) Laigret utilizes murine strain inoculated into the brain of mice. The Rickettsias are living but attenuated after desiccation of the brains.

Killed Vaccines (phenic acid and formol): (1) Weigl: intestines of lice infected rectally. (2) Zinsser (latest method): Rickettsias cultivated in the presence of tissues on agar. (3) Cox: Rickettsias cultivated on chick embryo. (4) Durand-Giroud: Rickettsias inoculated on rabbit or dog lungs.

The two last named killed vaccines have been used most frequently during the past few years (Cox's vaccine in the American Army, the vaccine of Durand-Giroud on 3,000,000 people). The protection appears good, but immunity lasts only a short time. It is advisable first to make three injections of 1 cc. at one week intervals and afterward to inject 1 cc. every six months if the risk of infection is great.

Brill's Disease

This disease, strongly resembling a classic but mild form of typhus (mortality from 1 to 2 per cent), was observed by Brill in New York in 1898 and later recognized as closely related to typhus, but appeared sporadically and without any relation to lice. Immigrant Jews coming from Russia and settling in New York or Boston have been those generally stricken by the disease.

Because of the experimental properties of the germ, Brill's disease is thought to be due to a late relapse of epidemic typhus (Zinsser). Yet there are other points not unlike endemic murine typhus.

(B) *Endemic Murine Typhus*

The disease is due to *R. mooseri.* The transmission from rat to rat is carried out by the rat flea, *Xenopsylla cheopis*, and the rat louse, *Polyplax spinulosus*.

From this animal reservoir, man is infected sporadically, more by contamination of skin excoriations by the excrements or the crushing of the fleas than by the bites.

Direct contamination by dried excrements of fleas is not excluded. The passage through the human lice is possible and can create epidemic conditions (Mexican Tabardillo).

The distribution is the same as that of the cosmopolitan rat: the southeast of the U.S.A. (Maxcy, 1926), and since then practically everywhere, including the Congo.

The disease resembles epidemic typhus but in an attenuated form, with less intense eruption, less petechiae, attacking the trunk by predilection, the nervous system only slightly, the prognosis being on the whole favorable (lethality 1 per cent). However, the Mexican Tabardillo is very serious.

The diagnosis makes use of the Weil-Felix reaction (OX 19) and the inoculation of the male guinea pig. The incubation is much shorter here than in epidemic typhus (4–6 days) and is followed after the onset by a

IMMUNITY CONFERRED TO THE GUINEA PIG BY THE PRINCIPAL RICKETTSIAL DISEASES

	Epidemic typhus	Murine typhus	Rocky Mountain spotted fever	Tsutsugamushi	"Q" fever
Epidemic typhus	+	+	–	–	–
Murine typhus	+	+	–	–	–
Rocky Mountain spotted fever	–	–	+	–	–
Tsutsugamushi	–	–	–	+	–
"Q" fever	–	–	–	–	+

THE WEIL-FELIX AGGLUTINATION IN PRINCIPAL RICKETTSIAL DISEASES

	OX 19	OX K
Epidemic typhus	+	–
Murine typhus	+	–
Rocky Mountain spotted fever	+	–
Tsutsugamushi	–	+
"Q" fever	–	–

plateau of 4–6 days. A characteristic scrotal swelling is seen (reaction of Neill-Mooser), with slight exudation in the vaginalis where the Mooser's bodies are found. These are large cells of which the cytoplasm is crammed with parasites. Certain strains of epidemic typhus produce a scrotal reaction on the first passage only, but the Mooser's bodies are missing. It is also possible to differentiate between epidemic typhus and murine typhus by inoculation of the rat. In the former case the infection is not apparent, in the latter there is fever and the condition may be serious. Plotz was able to distinguish by serology applied through cultivated Rickettsias the antigens of these two parasites.

Some of the cases described in the Congo under the name of Congo Red Fever appear as cases of murine typhus (Jadin).

The prophylaxis is based on the fight against rats (see further, the section on Plague).

(C) *Rocky Mountain Spotted Fever**

HISTORY

Clinically recognized in Idaho and Montana about 1890, Ricketts proved its transmission by the tick in 1906. In 1930, the existence of the disease in the East of the Continent was established and ultimately in most of the States of the U.S.A.

GEOGRAPHIC DISTRIBUTION

The disease exists in the majority of the states of the U.S.A. but particularly in the neighborhood of the Rocky Mountains (Idaho, Montana, and also Western Canada). It is associated with the typhus of Sao Paulo (Brazil) and no doubt with Tobia fever (Colombia).

ETIOLOGY

The disease is due to *Rickettsia rickettsi.* The reaction in the guinea pig varies greatly with the strain and it is independent of the latter in man. When the reaction is slight, the guinea pig develops the fever in four to five days, but shows no swelling of the scrotum. In its severe form, fever is high and the scrotal reaction, less exudative than in the case of murine typhus, produces fatal gangrene or, in cases which survive, an eschar. The disease may also be transmitted to the monkey and to the rabbit.

TRANSMISSION

This is conducted by ticks only. Rickettsia are found in the tissues of the tick, in the excrement, and in the eggs. Infection is therefore hereditary in the tick. Three natural transmitters are known: the wood tick, *Dermacentor andersoni* (the western form); the dog tick, *D. variabilis* (the eastern form); and *Amblyomma americanum.* Only the adult forms attack man; the larvae and nymphae infect rodents. Other ticks which would seem to be potential vectors are: *Amblyomma cajennense* and *D. occidentalis*, parasitic ticks of man; *Haemaphyalis leporis-palustris* and *D. parumapartus*, rabbit ticks; and *Rhipicephalus sanguineus*, the brown tick of the dog.

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* French: Fièvre pourprée des Montagnes Rocheuses.

It is probable that wild rodents (ground squirrels, field mice, etc.) in the United States form the natural reservoir for *R. rickettsi*, although this parasite has not been discovered among them up to the present time.

The "fiévre boutonneuse" of the Mediterranean basin is transmitted by the dog tick: *Rhipicephalus sanguineus*, and the dog is the reservoir of the virus.

In South Africa a similar disease is transmitted by the larval form of tick *Amblyomma hebraeum*, *Rhipicephalus appendiculatus*, *Haemaphysalis leachi*, and *Boophilus decoloratus*. They are fixed on grasses and become attached to a man as he walks through the savannah.

In Brazil the dreaded Sao Paulo typhus is transmitted by various *Amblyomma*. The reservoirs of the virus are the rat, together with the opossum, the domestic and wild dog, a wild rabbit (*Silvilagus*) and the agouti (*Dasyprocta*).

The tick fever of India, very closely allied to Rocky Mountain fever, is transmitted by ticks, probably *Rhipicephalus sanguineus*. A Rickettsial disease transmitted by ticks (*Dermacentor nuttali*) exists in Siberia.

PATHOLOGY

Macroscopically, one often finds scrotal necrosis and a marked splenomegaly. Histologically, the vascular and perivascular lesions resemble those of typhus: the arterial lesions are more severe, the nodules are less marked than in typhus, particularly in the brain where there are more often small infarcti. An exudative myocarditis is regularly found.

SYMPTOMATOLOGY

The disease strongly resembles typhus but the fever is of longer duration (three weeks); it frequently exhibits morning abatements and ends in lysis.

Eruption appears toward the fourth day in the form of pinkish maculopapulous elements becoming hemorrhagic. It appears on the wrists and ankles and spreads over the whole cutaneous surface including the palms and soles of the feet, the face and the scalp; the abdomen is at times only slightly affected.

The general symptoms recall those of typhus, the nervous system being quite often less affected. The frequency of gangrene of the scrotum, the prepuce, the tonsils, etc., are noteworthy, and related to the considerable lesions of the arterioles.

PROGNOSIS

It is severe but varies somewhat according to the strain: The disease is fatal in an average of 20 per cent of cases, and, as in typhus, is aggravated with age. The typhus of Sao Paulo is commonly very severe.

DIAGNOSIS

Diagnosis is clinically facilitated by the type of fever, the erythema, the definite splenomegaly. There is no primary lesion. Inoculation of the guinea pig creates a febrile infection which is frequently complicated by scrotal necrosis and produces no immunity against typhus or tsutsugamushi. The Weil-Felix reaction, somewhat modified, is sometimes clearer with Proteus OX 2, sometimes with OX 19. The Rickettsial antigen gives specific reactions.

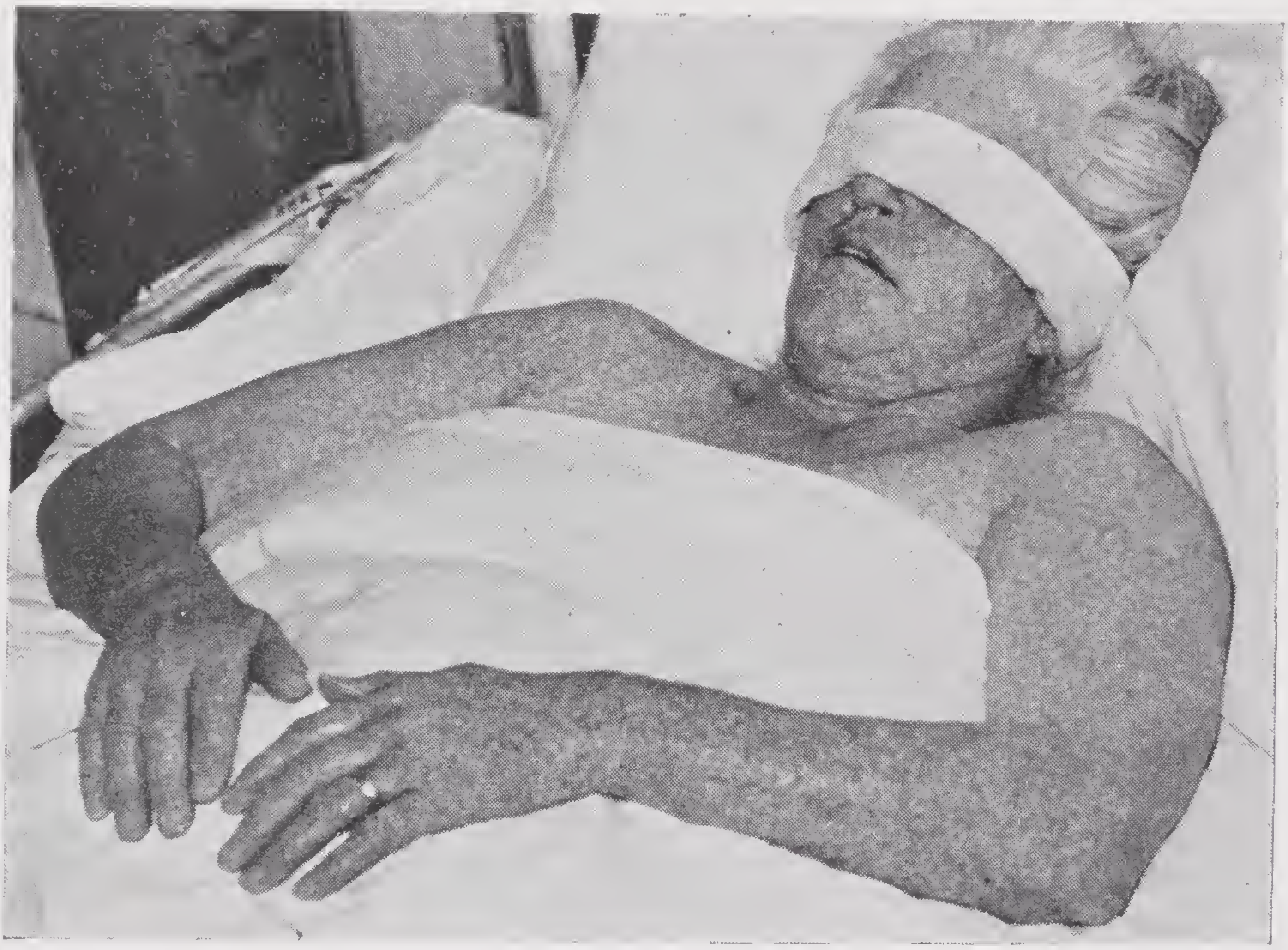

Fig. 28. Rocky Mountain Spotted Fever
Profuse macular rash on the eighteenth day of illness. Recovered (courtesy Dr. C. McGill)

Treatment: Acid p-aminobenzoic should be used.

PROPHYLAXIS

1. Man plays no part in the transmission.
2. Destruction of ticks by the use of insecticides has not so far been achieved, "Dipping" (generally an arsenical insecticidal bath), such as is used in the struggle against piroplasmosis and theileriosis in cattle,

reduces the number of ticks to an appreciable extent. The development of cultures has produced healthy conditions in certain regions of the United States (Bitter Root Valley).

3. A man who is called upon to move about out of doors can protect himself by the use of boots and hermetic clothing; by camping only in a cleared space far from suspected rodent burrows. In certain regions adult men are frequently the more exposed and this almost professionally (e.g., shepherds, hunters, but also, during the summer season, tourists).

In the East of the United States women and children are often found to be affected, which is doubtless due to transmission by ticks carried by dogs.

Vaccination against Rocky Mountain spotted fever (Spencer and Parker, 1925) gives real protection against the disease. It is excellent against the highly virulent strain of the Bitter Root Valley (seven laboratory workers who had not been vaccinated became infected and all died, while out of fifteen who had been vaccinated, only one died). The protection appears almost radical against the benign strain of Idaho (morbidity is 6 per cent among nonvaccinated shepherds and 0.5 per cent among the vaccinated).

Since 1940, the vaccine has been prepared from Rickettsias cultivated on chicken embryo using Cox's method.

In South America, similar methods of vaccination have been applied. The recommended injection is 1 cc. of vaccine, three times, at weekly intervals, and it appears to be necessary to repeat this each year.

Fièvre Boutonneuse

To this group is related a series of Rickettsial diseases also transmitted by ticks, but the clinical behavior is usually benign. These diseases have been observed in various countries, South Africa, Kenya, India, and possibly in the Congo, but the best known is the Mediterranean "fièvre boutonneuse."

Clinically this infection resembles the other Rickettsial diseases but as stated is more benign, the exanthema being generally like that of spotted fever.

The presence of a papulonecrotic lesion should especially be noticed, "tache noire" (black spot) appearing at the point of the tick's puncture and accompanied by a slight adenopathy. The prognosis is favorable (lethality 1–2 per cent).

The diagnosis must be made with the other Rickettsias. The attempt will be made to relate the primary lesion with the epidemiologic circumstances (contact with dogs, ticks, etc.).

The Weil-Felix is often slow (OX 19) or remains negative. A complement deviating reaction will distinguish this form from other Rickettsias, including spotted fever (Plotz).

Bullis Fever

The disease, observed at Camp Bullis in Texas in 1942–1943 is a fever of short or medium duration, with pains, adenopathy, pharyngeal exanthema, and at times an early and fleeting maculopapulous eruption on the trunk. Leukopenia occurs toward the second or third day.

The disease has been attributed to a Rickettsia which, immunologically, appears related to American Q fever. The disease creates no cross immunity with Colorado tick fever (see further).

The transmission is effected by *Amblyomma americanum.*

Rickettsialpox

In 1946 a peculiar febrile disease characterized by an initial lesion and an eruption of a vesiculopapular type was discovered in a housing development in New York City (Huebner, Stamp, and Armstrong). The name rickettsialpox was given because of a clinical resemblance to chickenpox and of the discovery in a patient of a Rickettsia, closely related to *R. conori,* the causative agent of fièvre boutonneuse, though serologically distinguishable. The epidemiologic study pointed out that house mice (*Mus musculus*) constituted the reservoir and that their blood-sucking mites (*Allodermanyssus sanguineus*) were the vectors of the disease. Several strains were isolated from the mites which proved to be culturally and serologically identical with the strain isolated from man. The name *R. akari* has been proposed (Huebner, Jellison, and Pomerantz, 1946).

(D) *Tsutsugamushi Fever*[*]

HISTORY

This disease has been known for centuries in China and also, it seems, the method of transmission. In Japan, too, its clinical recognition is of considerable long standing and it was there that European doctors (Palm, 1878, and Baelz a year later) learned to recognize it. Between 1920 and 1932 Japanese observers (especially Nagayo) elucidated the etiology. Pseudo-typhus (or Pseudo-typhoid) of Delhi was discerned in 1910 by Schüffner and colleagues. In Indo-China, Lagrange observed the first indisputable case (1923). Observations in Malaya, Australia, etc., have also defined the nature of various local diseases: scrub typhus, Mossman fever, etc.

GEOGRAPHIC DISTRIBUTION

This comprises almost the whole of the Far East, excluding China: India, Ceylon, Burma, Malaya, Sumatra, Japan, and the South West Pacific: New Guinea, Queensland. A large number of cases were seen during the military operations in the Pacific (1942–1945).

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[*] River Typhus of Japan, Pseudo-Typhus of Delhi (Sumatra), Scrub Typhus of Malaya, Mite Typhus. (Myte Koorts of the Dutch in Indonesia.)

ETIOLOGY

The disease is attributable to *Rickettsia orientalis*. This germ is only slightly virulent toward the guinea pig. It can be transmitted to the rabbit by intratesticular inoculation (interstitial cells) or by intraocular injection (endothelial cells of the cornea on the membrane of Descemet). Monkeys and rats can also be infected, but the mouse is the preferred experimental animal.

TRANSMISSION

In Japan the disease is transmitted by the puncture of the larva of an Acarian, *Trombicula akamushi*. In Formosa, in Sumatra, in the Philippines, in Malaya, and in Queensland, the transmitter is *Trombicula deliensis*, a kindred species, probably identical with the former.

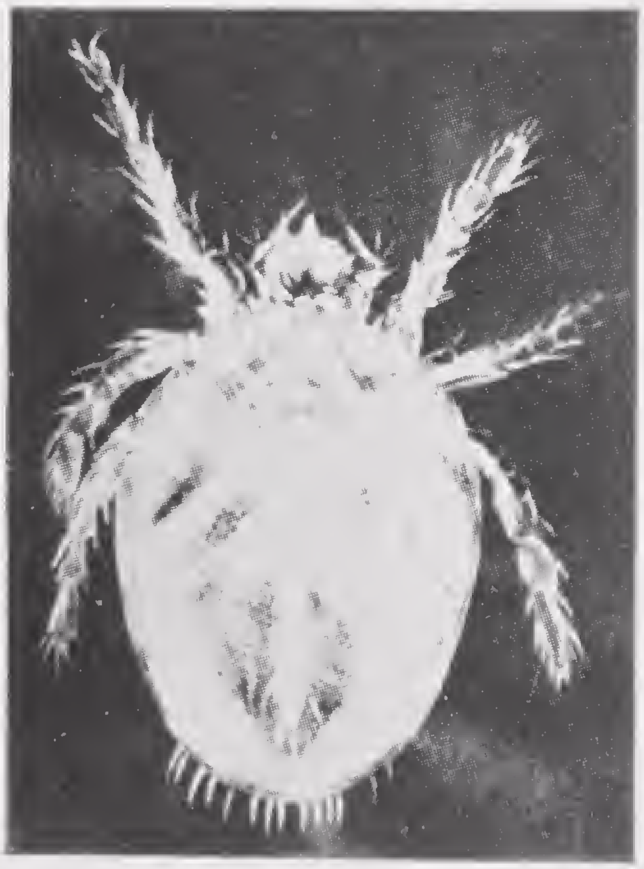

FIG. 29. TROMBICULA AKAMUSHI
Army Institute of Pathology, Neg. No. 8D4458, Washington 25, D. C.

The reservoir of the virus in Japan is the field mouse (*Microtus montebelloi*), in Sumatra, the house rat (*Mus concolor*) and field rat (*Mus viardii*), and in Malaya the house rat (*Mus rattus*).

The infection is hereditary in the Acarian. The latter becomes infected in the adult form in wild rodents. The larva is born from an infected egg. Of an orange color, it is hardly visible (it measures 400 μ by 200 μ approximately) and is hexapode (the adult possesses four pairs of legs and measures 1 mm. by 0.5 mm.). The larva only, which feeds but once, transmits the disease to man.

PATHOLOGY

Pathology strongly resembles that of typhus: vascularitis, myocarditis to the extent of necrosis, encephalitis, pneumonitis (inflammation of the alveolar walls), secondary broncho-pneumonia. A macrophage with basophilic cytoplasm is the characteristic element of the exudates in the myocard, spleen, liver, lymph nodes.

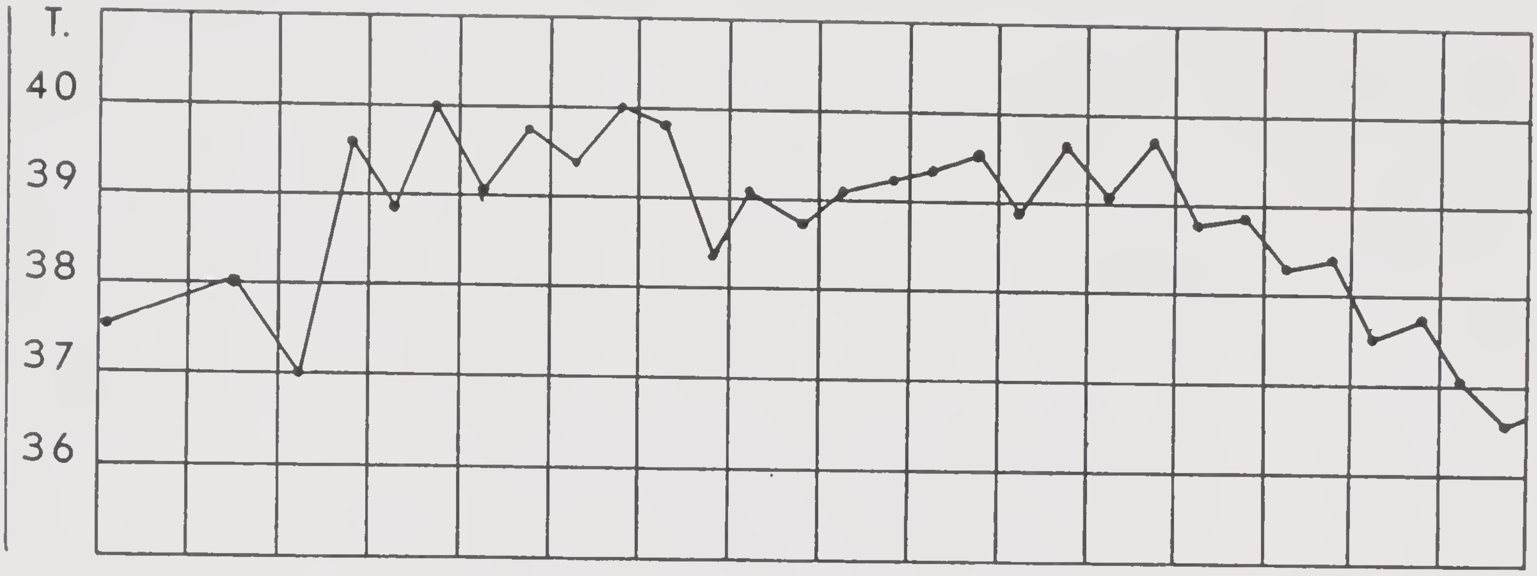

Chart 15. Scrub typhus in a Congo native of the Belgian Field Ambulance on the Burma front (Lieut. Louveaux)

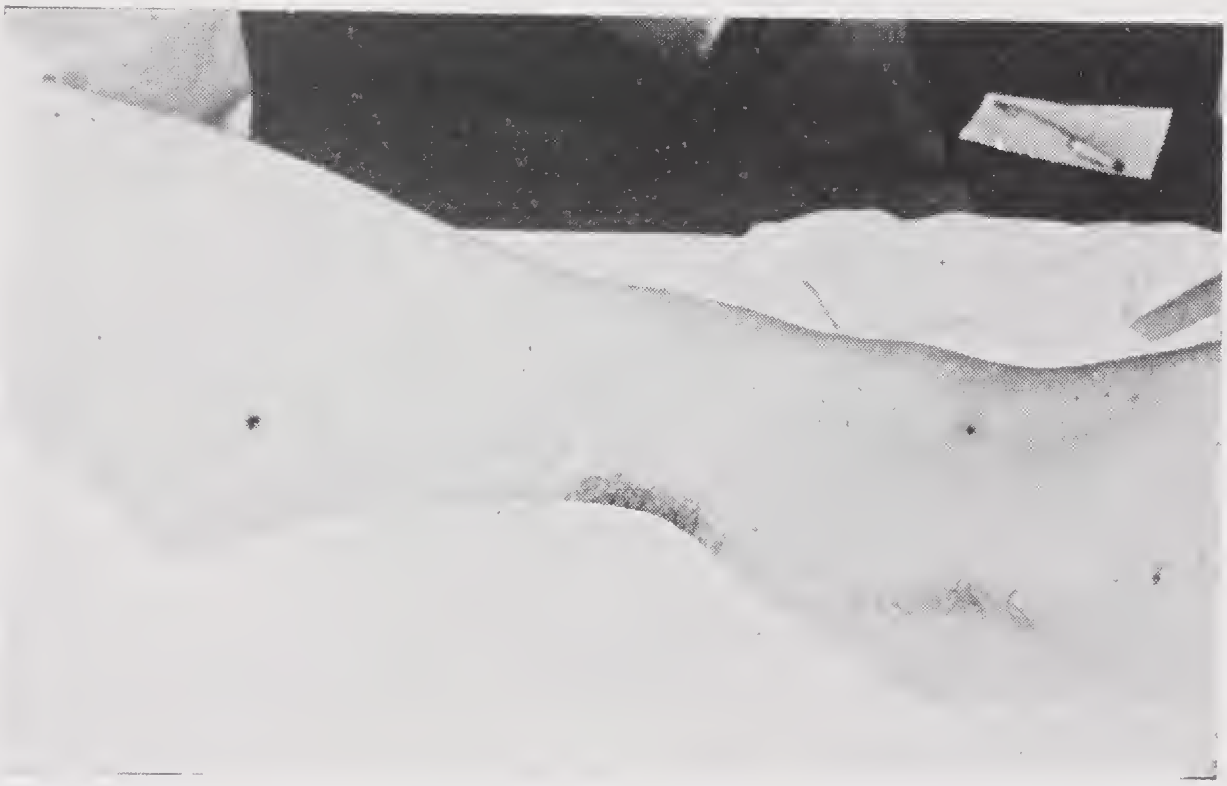

Fig. 30. Scrub Typhus: Two Initial Lesions
Army Institute of Pathology, Neg. No. D4445, Washington 25, D. C.

SYMPTOMATOLOGY

Incubation period averages fifteen days.

The symptomatology is very similar to rickettsial diseases: sudden onset, high fever, headache, eruption toward the fourth day and termination, more or less slow, after two weeks. Maculous or maculopapulous exanthema appears from the fourth to the eighth day on the trunk and spreads, excepting generally the extremities, and sometimes the face. It does not become petechial.

The nervous symptoms, the cough, the ocular congestion, and the myocardiac troubles are also of the rickettsial type. The anxiety is marked. Auditory and ocular troubles are fairly frequent. More characteristic is the existence of a primary complex: a papulonecrotic lesion (black spot) with adenopathy is almost invariable in tsutsugamushi, more rare in scrub typhus. General adenopathy is frequent. The usual complications arise (pneumonia, pleurisy, hemorrhages).

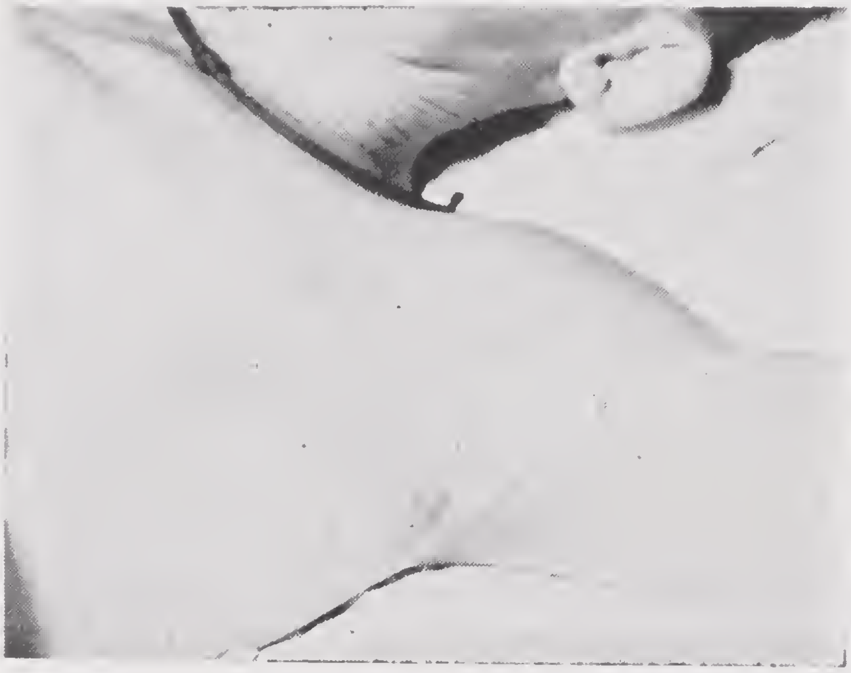

FIG. 31. SCRUB TYPHUS WITH AXILLAR INITIAL LESION
Army Institute of Pathology, Neg. No. D44165, Washington, D. C.

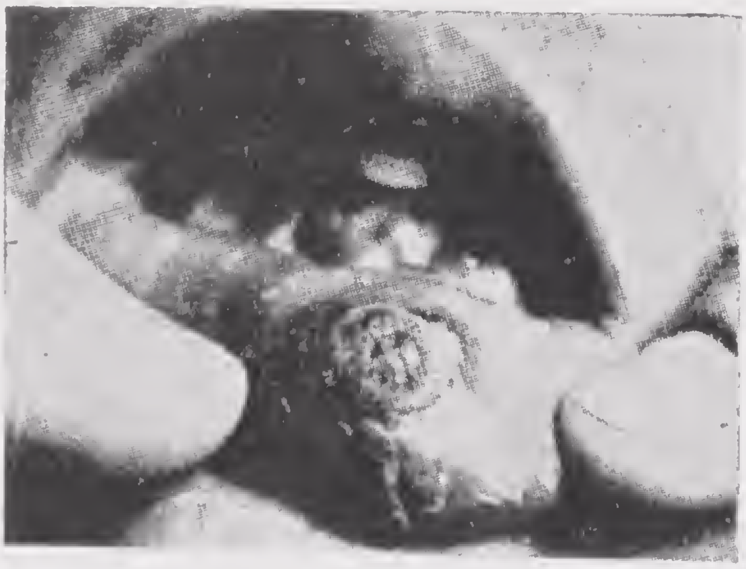

FIG. 32. PRIMARY LESION OF "MIJTEKOORTS" ON THE LIP IN SUMATRA
Courtesy Dr. W. Kouwenaar

PROGNOSIS

This varies from region to region, but is frequently severe (particularly in Japan), and on the average, fatal cases reach 15 per cent. Circulatory troubles of myocardiac or peripheral origin may persist for several months.

DIAGNOSIS

This will be facilitated by a knowledge of the endemicity, the epidemiology (contact with the soil itself on which acarians live), observation of the eschar (which may, however, be absent).

The reaction of Weil-Felix is confined to the OX K strain and, after the first week, may reach a high index, 1/100 being already significant. There is a considerable difference from typhus (OX 19) and spotted fever (OX 2–OX 19). Specific reactions (Rickettsias) may also be employed.

Treatment: The p-aminobenzoic acid seems even more active here than in typhus (see above).

PROPHYLAXIS

1. As the disease does not pass from man to man, isolation is of little importance.

2. The destruction of the larvae of Trombicula in nature is very difficult. Gammexane is more efficacious here than other insecticides.

3. Protection of a healthy man who must move in infested regions is best assured by the wearing of hermetic shoes and clothing, and by the use of dimethylphthalate on the skin, this affording efficacious repellent action for several hours. Impregnation of the clothing with this substance, with butylphthalate, and more especially with benzyl benzoate has been recommended as protection against Acarian larvae.

Vaccination, until recently, has been disappointing. A new dead vaccine using *R. orientalis* of a purified culture appears to be effective.

(E) *"Q" Fever*

HISTORY

Discovered in Queensland, from which the abbreviation may be derived*, this disease was discerned in 1937 by Derrick and related to the Rickettsias by Burnet and Freeman in the same year. Later, Dyer identified with the germ a Rickettsia found in the United States of America in the tick *Dermacentor andersoni* (Davis and Cox). In 1943, Caminopetros isolated a Rickettsia in the blood of German soldiers suffering from a fever of the influenza type in Greece, and the virus was identified in the United States with the same species.

GEOGRAPHIC DISTRIBUTION

It is probably widespread and, in any case, includes regions as different and as far apart as Australia, Southern Europe, and the United States.

ETIOLOGY

The disease "Q" fever (Queensland Fever) is attributable to *Rickettsia burnetti* in Australia, and *Rickettsia burnetti subsp. diaporica* in the

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* It seems that Derrick actually meant by "Q," *query*.

United States. The disease has also been recently discovered in Europe (1943, Mediterranean basin). These different sources are immunologically identical. Guinea pigs react more strongly to the American than to the Australian strains. They frequently die after two to eight days of fever (40.5 to 41 C.). Their urine is infectious. At autopsy one finds hypertrophy of the inguinal and mesenteric lymph nodes, a spleen increased in size and sometimes ruptured. When inoculated under or in the skin, guinea pigs exhibit inflamed swellings at the place of injection, with an exudate rich in Rickettsias. Inoculation of the mouse establishes small necrotic centers in the liver with the presence of Rickettsias in the Kupffer cells and in the spleen. The infection can also be transmitted to the monkey (*Macacus rhesus*) and to several marsupials and wild rodents of Australia. In the United States two rodents (*Eutamias* and *Citellus*) and in Morocco a squirrel and a hedgehog have also been successfully subjected to infection.

TRANSMISSION

The virus reservoir in Australia is a small marsupial the size of a field rat, the Bandicoot (*Isodon torosus*). The tick *Haemaphysalis humerosa*, in which the disease is hereditary, is the normal transmitter in the Bandicoot (this tick does not attack man, at least in the adult state and in nature), while *Ixodes holocyclus* and *Rhipicephalus sanguineus*, in which the infection is not hereditary, are the probable transmitters to man. These ticks discard numerous Rickettsias in their excrement. They also infect cattle. It is probable that man frequently becomes infected by inhaling dust laden with Rickettsias coming from the skin of cattle; this probably accounts for the frequent cases occurring among farmers and slaughterhouse workers (epidemic affecting 40 employees in a cattle ranch in Texas, 1946). In the Mediterranean, epidemics in armies (up to 30 per cent of the effectives) appear to have been due to direct transmission from man to man through droplets in the air and by mucous and respiratory introduction.

Dermacentor andersoni (Montana and Wyoming), *D. occidentali* (Oregon and California), and *Amblyomma americanum* (Texas) transmit the infection in the United States. The Rickettsia of "Q" fever was discovered in Morocco in the *Hyaloma savignyi* (Blanc, 1946).

PATHOLOGY

Little more than pulmonary lesions and splenomegaly have been displayed. The pulmonary lesions are of the interstitial type which are observed in virus pneumonia. There is leukopenia accompanied by lymphocytosis.

SYMPTOMATOLOGY

The period of incubation is from eleven to twenty six days. The onset is sudden, but without noticeable shivering, with the various customary discomforts. At times the disease develops like a fever sine materia for about ten days, sometimes twenty (this is particularly so in Australia); sometimes pulmonary symptoms also appear. Coughing, expectorating, sometimes with a small show of blood, are noticed. An examination shows faint sthetacoustic signs, but the x-ray reveals opacity. These phenomena are somewhat persistent and may continue after the apyrexia has otherwise disappeared. Pulmonary manifestations have frequently been observed both in Europe and in the United States.

"Q" fever is, as a rule, nonexanthematic.

Prognosis: It is benign. Rare fatal cases have, nevertheless, been observed (pulmonary manifestations).

Diagnosis: It is not clinically easy. The x-ray is useful but does not ensure precise identification of the pulmonary lesion. The latter may be due to virus atypical pneumonia, psittacosis, etc. Inoculation to guinea pigs and seric reactions are indispensable.

Treatment: The treatment is symptomatic.

Prophylaxis: The only practicable process in the event of a growing epidemic would be to use the vaccination which has proved efficacious in the guinea pig (Burnet and Freeman, 1939) but which has not been used to any great extent in man.

(F) *Trench Fever**

Definition: A fever of a recurrent type transmitted by the flea, characterized clinically by its benignity, its various pains, mostly in the tibia, and an eruption.

HISTORY

This disease seems to have appeared during the first World War in the squalid fighting areas (Flanders, France, and then Poland, etc.). Two English and American commissions demonstrated on volunteers that the blood of patients was infectious and that lice played a role in the transmission. The disease reappeared during the recent World War on the German-Russian front.

GEOGRAPHIC DISTRIBUTION

The disease was observed in most of the theaters of military operations during the 1914–1918 war, where it was extremely frequent (one-fifth of the illnesses). It appears to exist in Ethiopia (Codeleoncini, 1946).

ETIOLOGY

Man is the only known reservoir of the virus: the blood, the plasma, and sometimes the urine are infectious. The blood may continue to be infectious for as long as 300 days. The disease is usually attributed to a Rickettsia observed in lice that feed on sick persons. The relationship of this germ with *R. pediculi* of the normal louse is not clearly defined, both being extracellular in the insect. No seric proof either with Proteus or with Rickettsia has, up to the moment, elucidated the etiology of this disease.

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* French: Fièvre des Tranchees, Febris Volhynica; German: Funftage Fieber.

TRANSMISSION

This has been well established: lice which have fed on sick persons become infectious in about nine days. The crushing of lice, contact between dried excreta and skin abrasions constitute the normal method of contamination.

PATHOLOGY

Few sure autopsy observations of this disease have been made, beyond a histologic study of the spots: congestion, perivascular infiltration (lymphocytes and some polynuclears). There are no endovascular lesions of the typhus sort.

SYMPTOMATOLOGY

The incubation period varies between ten and thirty days. The attack is sudden, there is fever, algia, tibial pains, ocular pains, conjunctival injection. The temperature curve is very variable—sometimes a fever lasting a few days with relapses, sometimes a distinctly recurrent fever with attacks of short duration occurring at different times at intervals of several days (febris quintana). A prolonged fever is rarely seen. Relapses have been observed as much as one year or more later. The spleen is somewhat enlarged. A maculous eruption (rarely papulous) is frequently seen on the trunk. Functional cardiac troubles have been decribed. The muscles may be sensitive to pressure and anesthesia has been observed. Faint chronic sequelae have also been reported.

Prognosis: This is favorable, but convalescence is sometimes prolonged (generally two months, and sometimes more) and a degree of invalidity may persist.

Diagnosis: Clinically, no individual symptom is very characteistic, but together they are significant: fever with relapse, aches, exanthema, absence of catarrhal signs (influenza).

Epidemic myalgia (Bornholm's disease) is not connected with the lice. The symptoms of this short-lived disease are: fever (two to three attacks), myalgia, headache, benignity.

The laboratory here has only a negative value, i.e., in the elimination of various diseases: malaria, relapsing fever, leptospirosis, etc.

Treatment: Purely symptomatic; nerve tonics, rest, general hygiene.

Prophylaxis: See fight against lice (exanthematic typhus).

8. BARTONELLOSIS*

Definition: A disease appearing first in a febrile form (Oroya fever), then in favorable cases under an eruptive, nodular, or verrucous form (verruga peruana). It is caused by *Bartonella bacilliformis,* a parasite transmitted by Phlebotomes.

HISTORY

The disease appears to have been known for centuries in Peru and to have attacked the followers of Pizarro. In 1870, a severe epidemic smote the workers of the Lima-Oroya railway, from whence one popular name for the disease is derived. In 1885, Carrion, a Peruvian student, inoculated himself with the fluid of a verruga and contracted Oroya fever, justifying thereby, the unitarian concept held by the people in the country. After an incubation period of twenty-one days, he developed a mortal fever in sixteen days. In 1905 Barton discerned the organism of which Strong and colleagues (1913), then Noguchi (1926) established the role.

GEOGRAPHIC DISTRIBUTION

It is solely South American, chiefly in Peru, affecting, however, certain spots in Ecuador and Colombia, in the deep valleys of the Andes at altitudes varying between 800 and 3,000 meters.

ETIOLOGY

Bartonella bacilliformis was identified by Strong and the Harvard Commission in 1913 as the causal agent of Oroya fever as well as of verruga peruana, two syndromes of the same disease.

Bartonella are parasites of an indeterminate classification, closely related to Rickettsias. They are shaped like thin small rods from 1 to 2 μ in length by 0.2 to 0.5 μ in width, or rounded and measuring from 0.4 to 1 μ in diameter, or in V-form or also in Y-form (probably divisions). They are found in erythrocytes and the endothelial cells of the lymphatic cells and the internal organs in cases of Oroya fever, as well as in the endothelial cells of the cutaneous nodules of verruga.

Bartonella bacilliformis injected in the monkey *Macacus rhesus* develops a verruga. Culture has been successful on media for Leptospira (Noguchi), on various media containing living cells (cultures in tissues), as well as on fertile hen eggs (chick embryos).

Peruvian dogs exhibit a verruga which appears to have no connection with the human type of the disease, and which is due to *Bartonella canis.* Rats, splenectomized and carrying lice develop an exceedingly serious anemia from *Bartonella muris.*

TRANSMISSION

This has not, up to the moment, been determined with certainty. Phlebotomes (*P. verrucarum* and *P. noguchii*) have been incriminated.

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* Synonyms: Oroya Fever, Verruga Peruana, Carrion Disease.

Bartonella have been found in the proboscis of these Diptera and transmission to monkeys has been observed.

Bartonella canis is certainly transmitted by dog fleas *Ctenocephalus* and *Bartonella muris* by rat lice *Haematopinus* and the rat flea *Xenopsylla cheopis*.

PATHOLOGY

An essential anatomic sign of Oroya fever is considerable anemia: pallor of the organs, cardiac muscle pale and soft, liver and spleen voluminous, bone marrow red.

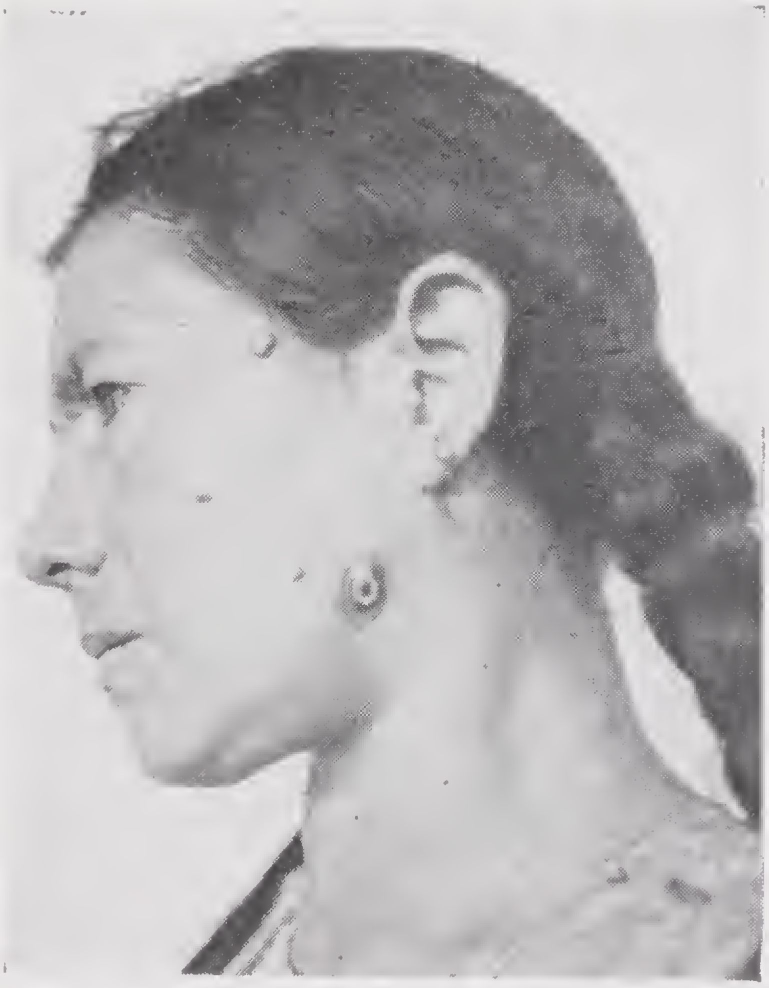

FIG. 33. VERRUGA PERUANA
Miliary and vesicular form from Colombia (courtesy Dr. E. Brumpt)

Bartonella bacilliformis invades not only the red globules but also the reticulo-endothelial and endothelial cells. As a result, one observes microscopically a hyperplasia of the cells filled up with Bartonella (liver, spleen, lymphatic ganglia, various capillaries).

Thrombosis, infarcti, erythrophagocytosis, and hemosiderosis are found.

The verruga has the appearance of a granuloma, very rich in dilated vessels. The staining of the Bartonella in the verruga is somewhat difficult. This lesion may become ulcerated or, on the contrary, may be completely cured. Hemorrhages are frequent. Histologically, there is sometimes a great resemblance with the angiomatosis of Kaposi.

SYMPTOMATOLOGY

After an incubation period of some twenty days, the disease appears, following slight feverish prodromes, as an irregular and remittent fever accompanied by various discomforts including aches in the bones. Macrocytic anemia becomes very severe and death may ensue in fifteen to twenty days.

If the patient resists, the verruga period appears during convalescence (three to four months after the onset), most frequently in the form of hemorrhagic spots turning into hard, round pimples with a strong tendency to hemorrhage (miliary form). Instead of a great number of papules, one sometimes finds nodules which are scarcer and of a deeper site (nodular form). The miliary form is mostly found on the arms, legs and face. The nodular form is generally seen near articular regions.

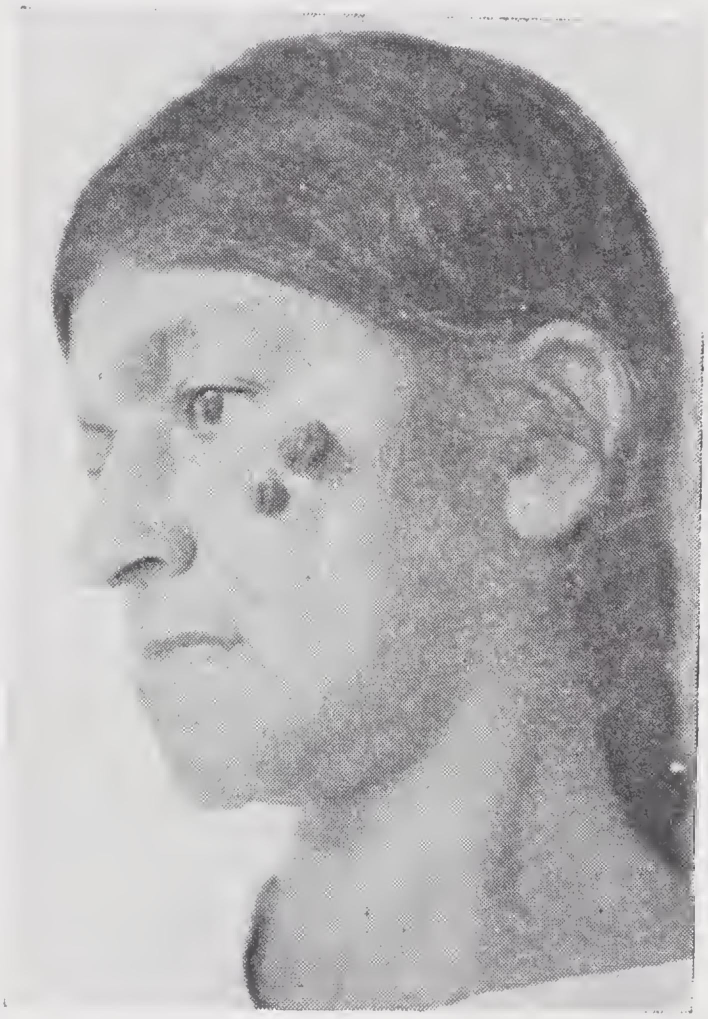

FIG. 34. VERRUGA PERUANA
Nodular form from Colombia (courtesy Dr. E. Brumpt, Hospital of Dr. Garanillo in La Union)

Prognosis: It is very severe in the febrile form and much more favorable in the cutaneous form. Children, but also certain adults, present mild cases. The average fatality of Oroya fever is from 10 to 40 per cent.

Diagnosis: During the feverish stage, diagnosis is clinically difficult, but an examination of the blood under the microscope, or by cultures, will normally solve the problem. Clinical diagnosis of the eruption seems comparatively easy, at least in an endemic region.

Treatment: Neoarsphenamine, effective against Bartonellosis in the rat, seems useless in man.

In experimental work Kikuth found a favorable reaction in the rat to an arseno-antimonial product, Sdt 386 B. But again in human medicine the result appears to be negative. Penicillin seems to have brought some success.

Prophylaxis: This consists for the individual in avoiding the endemic area after nightfall, or, at least, in remaining at that time in a room protected by mosquito nets of a very fine mesh. The destruction of Phlebotomes by means of insecticides appears difficult in the narrow valleys of the Andes between 800 and 3,000 meters (from parallel 2 North to 13 South) where the endemic centers are found. The action of DDT on Phlebotomes (see kala-azar) should be recalled.

Active immunization by the injection of cultures of Bartonella offers no protection against infection, but appears noticeably to diminish the clinical picture (Howe and Hertig, 1943).

9. PLAGUE*

Definition: An endemo-epidemic disease caused by the plague Bacillus (*Pasteurella pestis*, Yersin bacillus) transmitted from the rat to man by fleas. The disease is characterized by buboes and infectious phenomena, frequently serious and even septicemic. There is a pulmonary form which is transmitted by inhalation. Nonpulmonary plague is sometimes predominant in man and his lodger, the rat (human plague and domestic zooplague), sometimes in wild rodents and in a few human beings (sylvatic plague).

HISTORY

The plague was without doubt observed in the Near East in the pre-Christian era. Mention is made of it in the Bible (Samuel), reference even being made to an epizootic disease among the Muridae. Dionysius (third century B.C.), Rufus of Ephesus (first century B.C.), and Dioscorides (beginning of the Christian era) describe with more or less precision the buboes and the resultant mortality during epidemics in Egypt or Lybia. Procope describes how in 540 A.D. the so-called Justinian plague traveled from Egypt and ravaged the states of the Byzantine Empire. It appears to have reached Western Europe, where Gregory of Tours called it "mal des aines" (illness of the groins). The epidemiology of it appears obscure because the presence of the rat in Europe at that time is problematical. Nevertheless, the first indisputable epidemic in Europe is that which raged from 1345. Mortality was enormous, the terror indescribable. Guy de Chauliac, physician to the Pope of Avignon, to whom we owe an excellent description, writes that a father refused to visit a sick son, and vice versa. In London, there were 100,000 deaths and, a thing apparently no less fearful, an invasion by the Scots. This epidemic was the Black Death; whether this name was purely imaginary or referred to ecchymosis and gangrene is not known. This widespread infestation of the fourteenth century was contemporaneous with the first invasion of Europe by *Rattus rattus*, an invasion surely more deadily than most of those described to us by historians. Epidemic followed epidemic in Europe up to the seventeenth century (the Great Plague of London, 1665), but the disease withdrew toward the East in the eighteenth century. Napoleon encountered the plague during the siege of St. John of Accra. In 1893, spreading from Yunnan, the plague reached Hong-Kong, then in the course of several years invaded the entire world, leaving the existing centers. Yersin discovered the bacillus in Hong-Kong (1894). In 1910 and 1911 a serious pulmonary epidemic reigned in Manchuria. In 1920 a fairly mild epidemic among the poor quarters at the periphery of Paris was noted.

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* French: Peste; German: Post.

GEOGRAPHIC DISTRIBUTION

The Asiatic seat is still the most important: India (where the disease is on the decline), Indo-China, Indonesia (Java), various Chinese provinces, Iraq, the shores of the Caspian Sea. Europe is almost immune. In Africa a few cases are found everywhere: North Africa, West and East Africa, Madagascar. The Congo is scarcely affected; two small centers are known to the West of Lake Albert and Lake Edward. But it seems that in this section the plague is very much of the sylvatic type as is the case in South Africa, Uganda, etc., that is to say, that it has become adapted to wild rodents. Australia is free from plague. In the Americas the region of the Andes is affected, Chile, Peru, etc., and various other countries; in the United States the plague has become sylvatic in California and, from time to time, gives rise to small epidemics or rather to sporadic cases. Sylvatic plague is encountered in Argentina (Cordoba province).

ETIOLOGY

Pasteurella pestis (Yersin, 1894) is a coccobacillus, immobile, Gram-negative, frequently of bipolar staining. The pleomorphism is noteworthy: involution forms in discs, rings, clubs, are common.

Culture, aerobic or anaerobic, is fairly easy. The broth remains almost clear, with a deposit of small clots. In broth covered over with oil, the bacilli form stalactites. There is no exotoxin, but after a considerable period endotoxin is liberated. Glucose, maltose, mannitol, and salicin are acidified without gas. Indol is not produced.

The bacillus of the plague is extremely pathogenic for most animals, especially rats, mice, and guinea pigs. The bacillus may contaminate transcutaneously. Resistance in the outer world is somewhat weak.

The virus reservoir is principally animal: wild rodents, *Citellus beechyi* (California ground squirrel), *Arctomys bobac* (tarbagan in Central Asia), *Spermophiles* (Russia), *Taterona lobengulae* (Gerbilles, in South Africa), etc. This reservoir maintains the sylvatic zooplague, better called selvatic (wild rodents plague).

Side by side with the former there is a reservoir of domestic zooplague: *Rattus rattus* and its varieties, *Rattus norvegicus, Mastomys coucha.*, etc. Field mice (*Arvicanthis abyssinicus*) in Africa, for example, may possibly be the intermediary between the two zooplagues.

The human reservoir, on the contrary, is of little importance, except in cases of pulmonary localizations, where direct transmission by coughing, etc., is the rule.

TRANSMISSION

Except in respiratory localization, this is effected by the bite of rat fleas: *Xenopsylla cheopis* and *brasiliensis* principally. The semi-blockage of the proventricule of these fleas by colonies of microbes constitutes a lively mechanism for transmission, as the insect is compelled to make repeated punctures, many being fruitless, thus leading to infectious regurgitations. The human flea (*P. irritans*) is an occasional transmitter. Epidemiology depends upon the relationship between man-rodent-flea. From this point of view *Rattus rattus*, being more "domestic," is of greater effect than *R. norvegicus*, as an epidemic factor, *R. norvegicus* having greater influence on the persistence and spread of the disease. It is noteworthy that the plague center of Lake Albert has, up to the present, been free of *Rattus rattus*, which is replaced by *Mastomys coucha ungandae*. *R. rattus alexandrinus* is, on the other hand, common at Lake Edward (as it is throughout the Belgian Congo, from which *R. norvegicus* is absent).

Climate has a fairly important effect: fleas become rarefied in very hot, dry months, and also in cold periods. A humid and cold climate seems essential for the transmission of pulmonary plague (survival of bacilli, greater tendency to overcrowding in houses). One can imagine pulmonary plague appearing only after the occurrence of cases of bubonic plague, a certain number of which produce secondary broncho-pneumonia, origin of the pulmonary epidemic.

The other forms of contagion are of little importance (clothing, contagion during nursing, autopsies, etc.).

Human beings have not been clearly established as germ carriers. Immunity is uncertain.

PATHOLOGY

As is the case with all animal Pasteurelloses, the plague is a general infection transmitted through the lymph and often through the blood. Autopsy serves to ascertain the considerable attack on the lymphatic ganglions either at the point of inoculation or at some remote place. The adenitis is of an acute type with hemorrhagic and necrotic periadenitis. In addition, one finds the lesions of acute septicemia: congestion, cutaneous, serous and visceral hemorrhage, alteration of the capillaries, degeneration or necrosis of various parenchyma (small necrotic nodules of the liver, soft and congested spleen).

The lungs are congested and hemorrhagic. Frequently there is pleural exudate. With extreme frequency the lungs display foci of alveolitis, of lobular or lobar appearance. Under the microscope, necrosis predominates over cellular infiltration and the number of bacilli is enormous; fibrin is absent. Normally the heart is dilated and the fibers degenerated.

SYMPTOMATOLOGY

Incubation, normally quiet, is short: two to nine days, most frequently three to four.

The most frequent clinical forms are:

1. *Major Bubonic Plague.* The onset is sudden or rather sudden with shivering and a rapid rise to high or very high temperature. The face is congested, of an inebriated appearance, the eyes bloodshot. The heart is rapid, and the pulse feeble and dicrotic. The nervous system is strongly affected: intense headaches, difficulty in hearing, rachialgia, excitement, delirium or somnolence; in the case of children, convulsions. Urine is scarce and sometimes shows traces of albumen.

To these fairly common signs of serious infection are frequently added lymph ganglionic signs from the second or third day. The plague bubo is an acute adenitis accompanied by periadenitis producing severe pains with a sometimes antalgic attitude. It is most frequently situated in the groin but may be found in the armpits, in the neck, etc. If the patient survives some time, suppuration will appear.

On the skin may be observed a vesiculo-necrotic lesion (plague carbuncle) which may represent a primary lesion. Other plague carbuncles correspond to secondary localizations on the skin. An angina has also been noted as a primary lesion. It would appear in certain cases to be the result of the habit of natives of crushing fleas between the teeth. One might also consider, in this case, contagion by a subject displaying pulmonary localizations. The development of the disease is rapid. Very often the fever lasts only a few days (5–6) and the patient succumbs during the collapse. Sometimes the fever continues for ten to fifteen days, the bubo suppurates and the patient finally recovers. He may, however, undergo a painful convalescence, paralyses, etc. (plague marasmus).

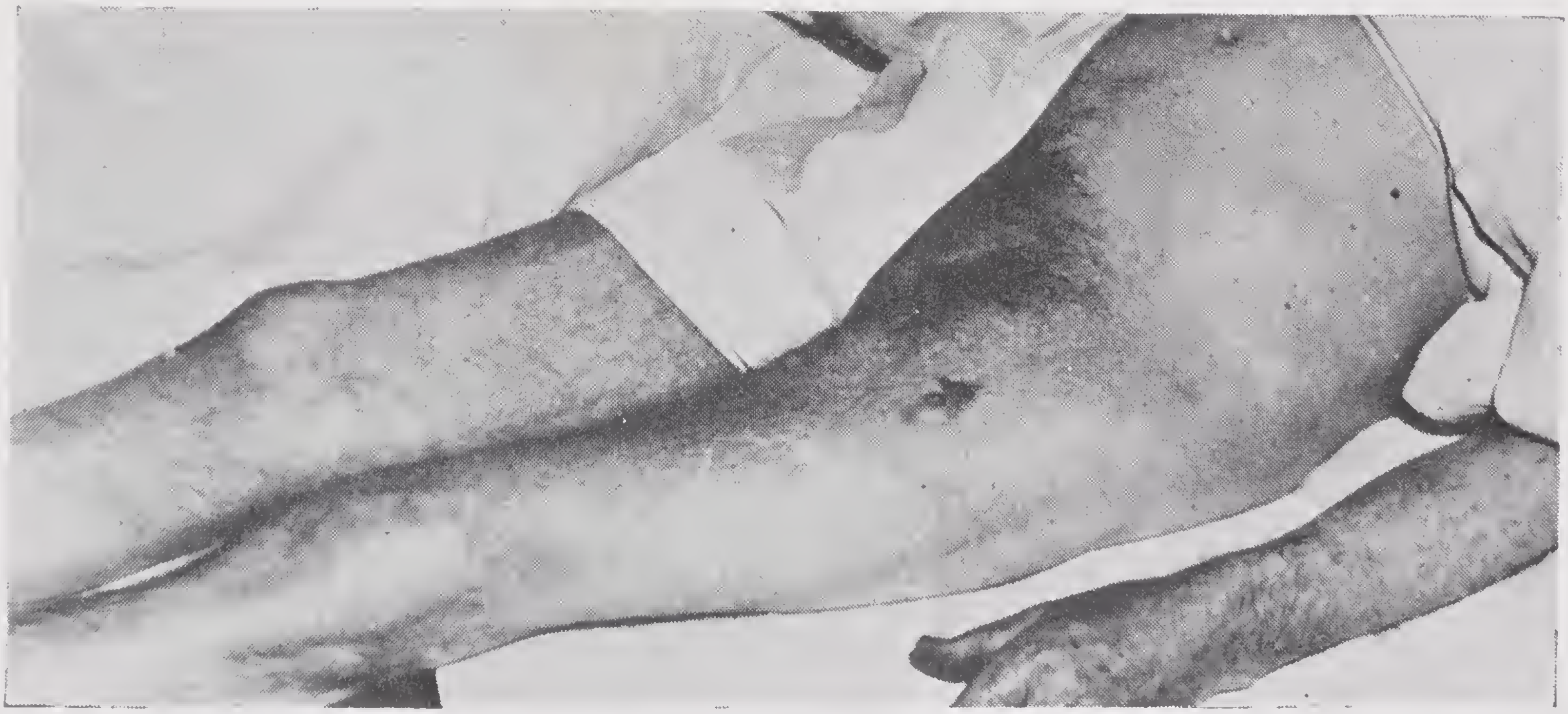

Fig. 35. Plague
Primary skin lesion (courtesy Dr. K. Meyer)

Various complications may be observed: plague broncho-pneumonia, miscarriage and, in addition, suppuration, septicemia, cutaneous gangrene, etc. Papulovesicular exanthema has also been noted.

2. *Minor Plague.* This form carries all the symptoms of bubonic plague, but reduced to such an extent as to allow ambulatory cases.

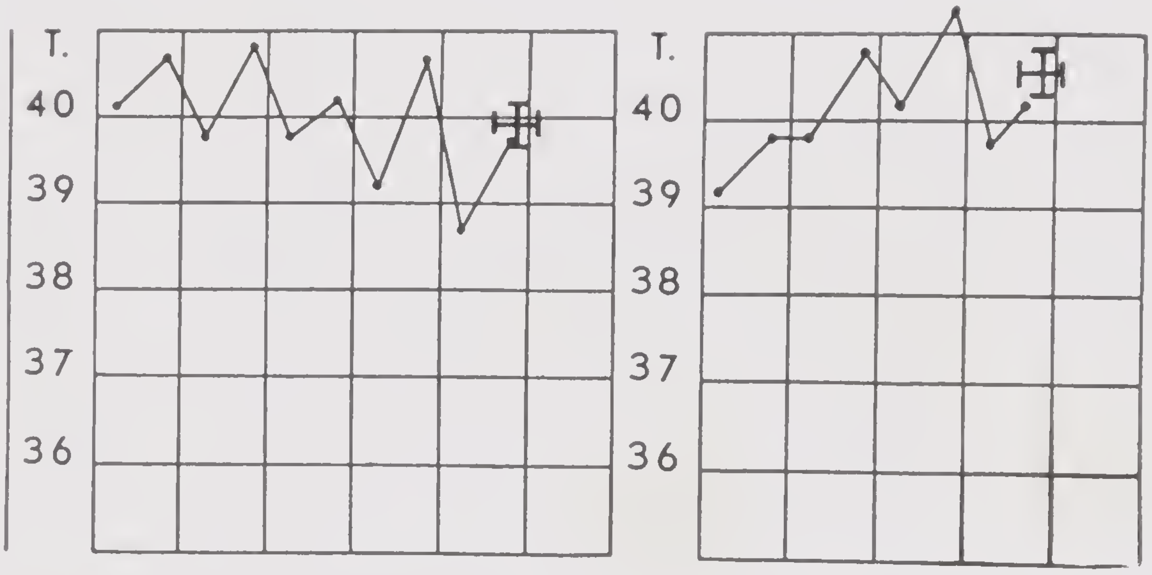

CHART 16. Two fatal cases of bubonic plague (semischematic)

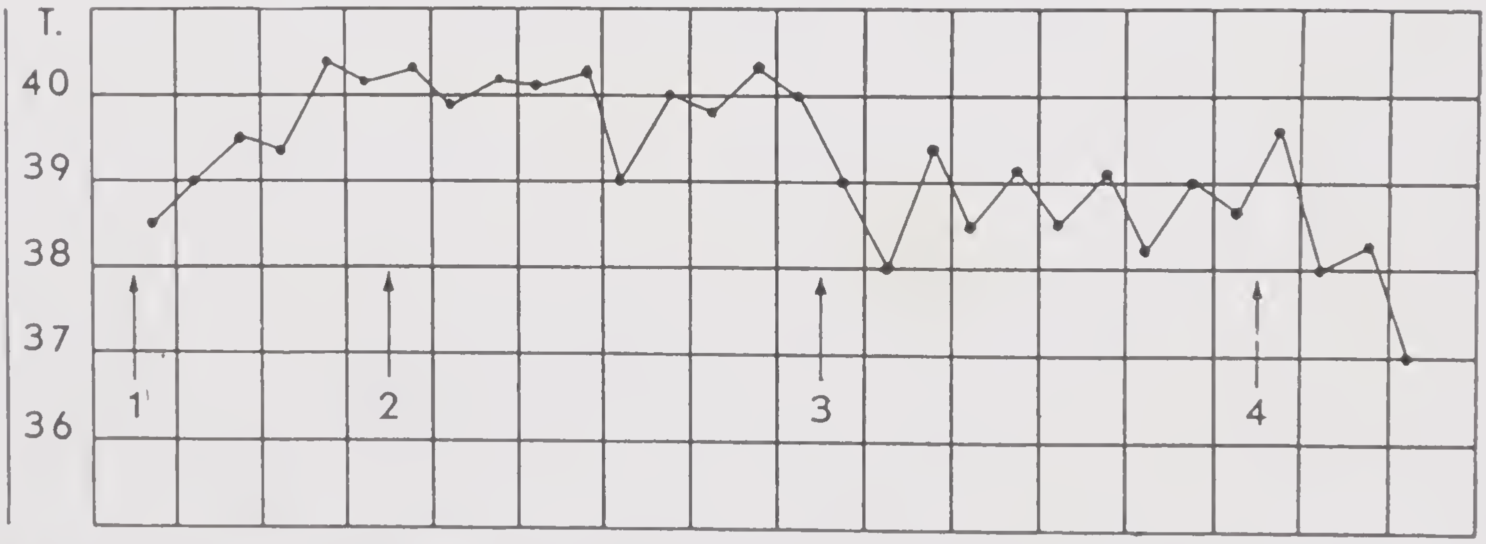

CHART 17. Bubonic plague from Morocco with recovery: (1) sharp onset; (2) appearance of inguinal buboes; (3) maturation of the buboes; (4) spontaneous opening of buboes (Dr. Blanc)

The general symptoms are mild, the bubo may not suppurate, and the prognosis is favorable. Clinical diagnosis, on the other hand, will be difficult.

There may even be healthy carriers. However, these subjects would offer little danger epidemiologically, through the probable absence of septicemia and, consequently, of the possibility of infecting fleas.

3. *Septicemic Form.* This applies to very serious cases where these general phenomena predominate and in which the adenites have no time to appear. Hemorrhage and ecchymoses are considerable (black plague).

Pulmonary localizations or meningitis are almost the rule. "Primitive" plague-meningitis, though rare, has been noted. Death invariably ensues.

Diagnosis, further facilitated by information on the endemo-epidemiology, is possible only bacteriologically.

4. *Pulmonary Plague.* By this is understood the primary manifestation of plague and not the frequent secondary localizations of bubonic plague. The latter originate from the former. But once established, pulmonary plague is transmitted by direct contagion with terrible rapidity. After a very short period of incubation (2–3 days) there is a feverish

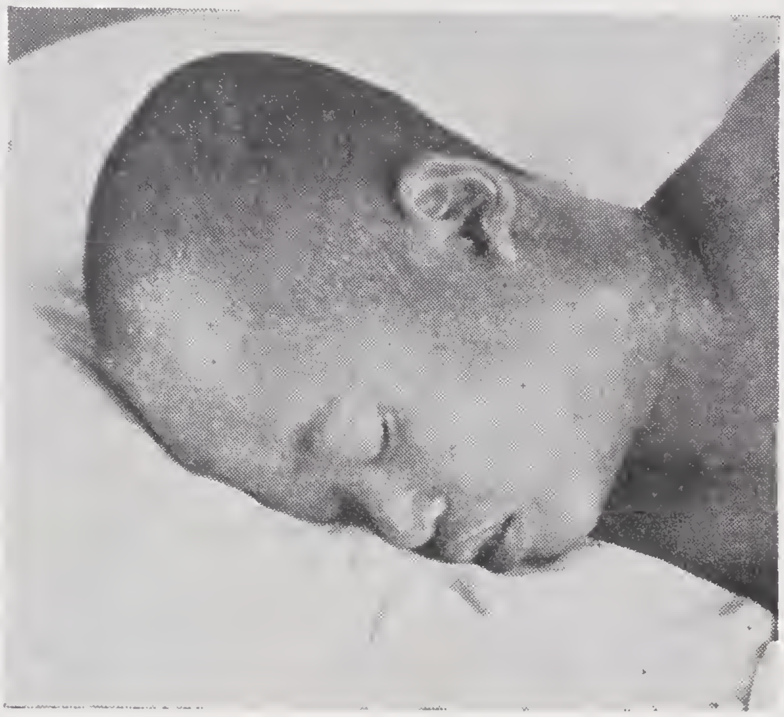

Fig. 36. Plague
Cervical bubo (courtesy Dr. E. P. Snijders, Indisch Instituut, Amsterdam)

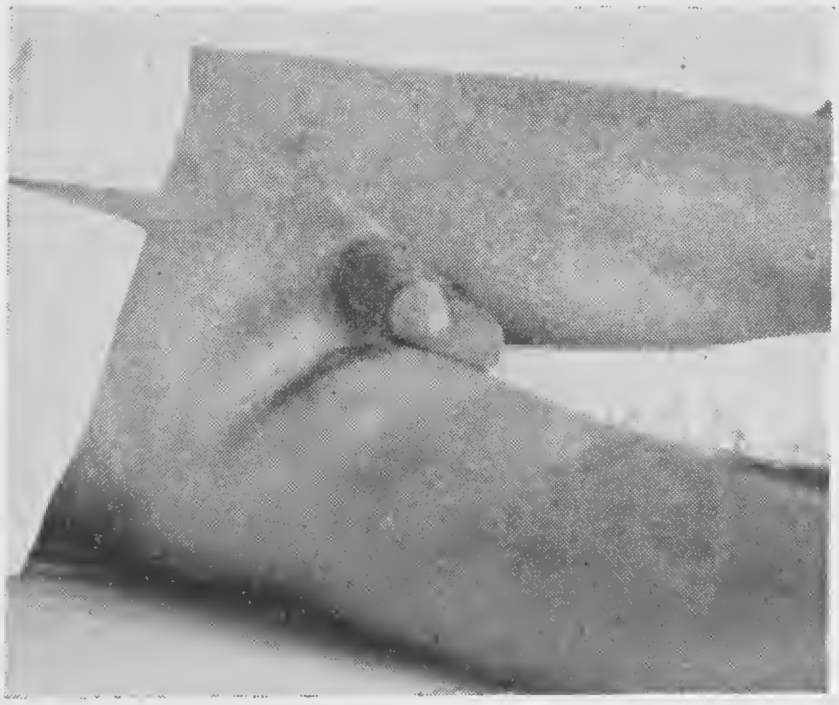

Fig. 37. Plague
Inguinal and crural bubo (courtesy Dr. E. P. Snijders, Indisch Instituut, Amsterdam)

onset with various discomforts. Functional respiratory signs rapidly appear: cough, dyspnea, expectoration displaying eventually mucus, or serum and traces of blood. Stethacoustic signs are slight or those of broncho-pneumonia. Diagnosis will be established by the extreme contagiousness and the rapid and fatal course of pneumonia-plague, which makes this disease the most dreaded of respiratory infections.

5. *Cutaneous Plague.* This form rather lacks individuality. It is characterized in the midst of an infectious syndrome by the development of extensive cutaneous eschars, found chiefly at points of pressure. It is due to the spread of plague infection to the skin and it is possible to find the bacillus in the exudate of the lesions. These are late localizations.

It seems that the eschar sometimes corresponds to an extension of the small inoculation lesion mentioned above and may therefore appear early and singly.

PROGNOSIS

With the exception of minor plague, prognosis is altogether unfavorable. Average mortality of bubonic plague is 50 per cent. The septicemic and pulmonary forms are almost always fatal.* Cutaneous plague has a better prognosis in cases of primitive cutaneous plague, but less so in cases of secondary multiple lesions. A prolonged fever, suppurations of the buboes are the attributes of resistant cases. Very high temperatures, sudden falls with collapse, a rapid pulse are grave signs. The discovery of positive septicemia is also unfavorable, particularly if the microbes can be directly discovered under the microscope. Axillary or cervical buboes appear to produce more pulmonary or septicemic complications, while the rare submaxillary buboes may be accompanied by glottal stenosis.

DIAGNOSIS

Typical bubonic plague is easily diagnosed. The epidemic, the buboes, and the mortality form a characteristic triad which distinguishes plague from common adenitis, venereal infections, or Nicolas-Favre disease. These diseases never have the extensive toxemia of the plague. The first case might be less easily diagnosed, however, and should be confirmed by laboratory examination; this latter is indispensable in cases of minor plague. Tularemia is less serious and of longer duration. It is not known in tropical countries. Septicemic plague can be diagnosed only bacteriologically. Pulmonary plague is characterized by its serious nature and its rapid development by contrast with the comparative insignificance of objective signs. Nevertheless, here, also, recourse to the laboratory is desirable.

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* Munter (1945) cites one cure (pulmonary plague) of a vaccinated case treated with sulfadiazine.

Laboratory Diagnosis

The plague bacillus is sought (1) in the patient: puncture of the lymph nodes, examination of the expectoration, hemoculture. (2) On the corpse: puncture of the bubo, the liver, the lungs, and the bone marrow. (3) In rats: Autopsy on rats will be made after immersion in soapy cresol. Special attention will be given to signs of septicemia, suppurated ganglion (cervical) pleural effusion, mottled liver, congestion and cutaneous hemorrhage. The bacilli will be looked for in the bubo, the spleen, the blood of the heart, and preferably in the bone marrow of the femur. (4) In fleas: by inoculation of guinea pigs.

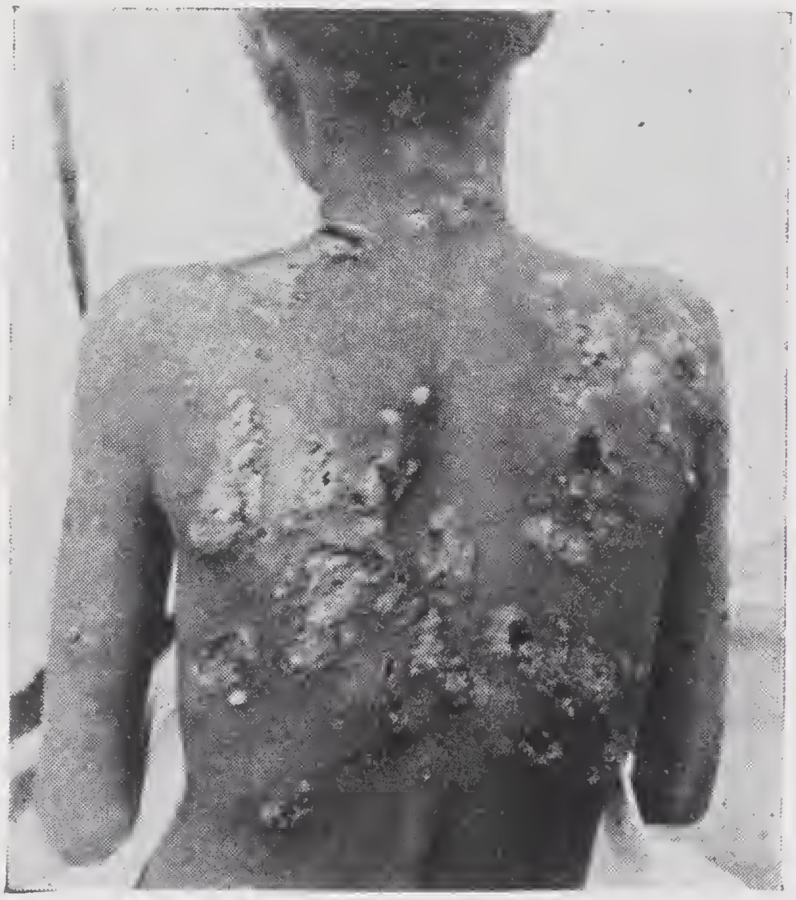

Fig. 38. Plague
Skin lesions (courtesy Dr. E. P. Snijders, Indisch Instituut, Amsterdam)

Identification is established: (1) By microscopic examination: shuttle shapes, disc shapes and rings in the decomposed material.

(2) By inoculation of the guinea pig or mouse subcutaneously and transcutaneously. This latter process is effected by rubbing the infected material on the roughly shaved skin which is consequently somewhat scratched. It has the great advantage of being carried out with putrefied material. Only very virulent bacilli, particularly Pasteurella, will infect under these conditions. It is, however, less effective than subcutaneous injection. Infection may also succeed by the transconjunctival route.

(3) By culture: In the Congo, injection is made of a series of femoral marrows of the rat into a single guinea pig, with a view to determining the endemicity. The infectious material (fragment of organ, bone marrow, fleas) is best preserved in the following liquid (for at least six days):

Neutral glycerin	20 cc.
Water	80 cc.
Calcium carbonate	2 Gm. To be sterilized.

It is to be remembered that plague usually produces notable polynucleosis.

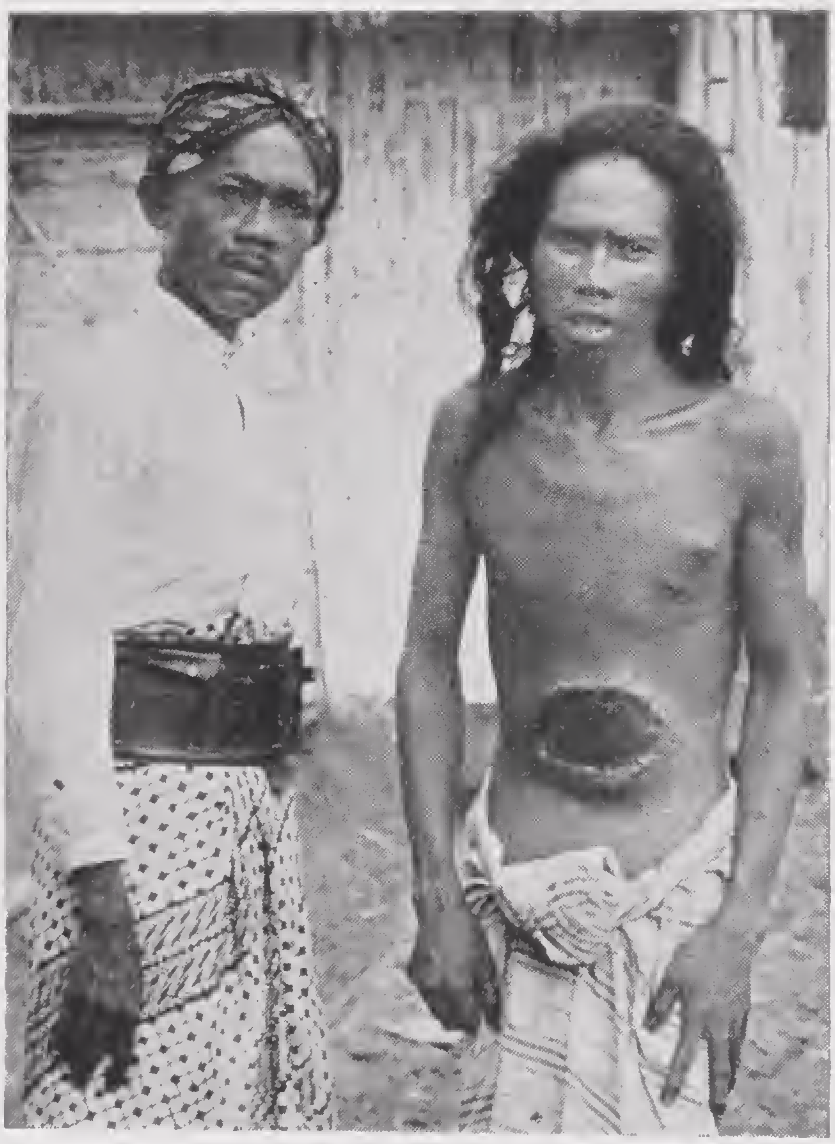

FIG. 39. CUTANEOUS PLAGUE
Courtesy Dr. E. P. Snijders, Indisch Instituut, Amsterdam

TREATMENT

The early administration of serum in high doses 100 cc. at a time (in all 300 to 400 cc.) may be useful in the bubonic form. It is associated with the bacteriophages.

At the present writing the most effective treatment was sulfathiazol, or better still, sulfadiazine in large doses: 15–20 mg. per 100 cc. blood should be maintained for four to five days. The excretion of at least 1500 cc. of urine should be ensured. Otherwise, symptomatic treatment is common. The bubo will be tapped when fully developed.

Streptomycine displays a marked activity in vitro and in vivo. Human cases, even pulmonary, have been cured with ease (verb. com. Carl Meyer). The dosage actually used is 1 Gm. per day for ten days.

PROPHYLAXIS

Bubonic Plague: (1) Human reservoir: strict isolation should be imposed in view of the possibility of pulmonary localization (though contagion is less marked in warm countries) and treatment as in a pulmonary case.

(2) Animal reservoir: destroy rats; employ cats and ratting dogs; utilize concrete constructions to avoid rats. Prevent their access to food storage and refuse dumps so as to limit the reproduction of rats. In small native huts, destruction is very difficult: cats may be employed, and also poison, but the latter is not very effective in respect to animals which have so many opportunities of finding food to their liking. Barium carbonate has been widely used: a mixture of 1 kilo of the poison with 3 kilos of flour, made into 5,000 pills each equivalent to 200 mg. of carbonate.

A paste containing 0.75 per cent of Phosphuretted Zinc is highly recommended. The most active product of recent times appears to be Monofluoroacetate of Sodium. This substance is highly toxic to man (8 mg. per kilo being fatal).

Pathogenic germs appear to form an uncertain combatant against rats, and may not be altogether without harm to man. On board ship, hydrocyanic acid is the most effective substance, but it is also the most dangerous to man. Sulphur dioxide may also be used (Clayton apparatus). The selvatic reservoir is difficult to attack.

(3) Fleas: the fight against insects demands cleanliness in the house, washing with cresol solutions, etc.

(4) Healthy human beings: vaccination provides certain protection. Avirulent live strains have been mostly used (strain Otten "Tjiwidej" or strain E. V. of Girard and Robic, Madagascar). They were considered as more efficacious than dead bacilli (such as the broth grown, heat killed Haffkine vaccine).

Recently, however, the agar-grown, formalin killed plague vaccine (U. S. Army) has proved to be highly efficacious. One-half cc. and 1 cc. are given seven days apart (2,000 millions per cc.). Repeated booster doses are always imperative, at least every three months for subjects exposed to infection.

For Pulmonary Plague, hospital personnel should be protected by masks, glasses, blouses, gloves. Sero-vaccination should be given to such personnel (10 cc. of serum at the same time as the vaccine). Avoid all skin abrasion (in shaving, for example). Ensure strict isolation of patients.

10. TULAREMIA

Although this infection is quite the opposite of tropical it must be mentioned because of its possible confusion with plague.

Definition: Septicemia of rodents, etc., caused by *Bacterium tularense* or *Pasteurella tularensis*. May be transmitted to man by accidental inoculation or insect bite. Clinically, there is a combination of general phenomena and a lymphatic complex with the possibility of septicemia and secondary localizations.

HISTORY AND DISTRIBUTION

The disease of the Citellus was discovered at Tulare (California) by MacCoy in 1911. Later research, particularly by Francis, defined its pathogenic role as regards man. The disease has been observed principally in the United States of America (in almost every state), Japan, Russia, Scandinavia, Central Europe, Turkey, France.

ETIOLOGY

The germ is a small immobile coccobacillus, Gram-negative, and aerobic. Its culture requires special blood or egg media, and more especially cystine. It is pathogenic for the guinea pig, etc.

TRANSMISSION

The animal virus reservoir is the most important: hares and rabbits, Citellus, rats, Castor, to which the disease is transmitted through various insect bites (ticks, diptera, etc.)

Man is infected either by these insects or by direct contact with infected animals during skinning (hunters, etc.).

PATHOLOGY

The appearance of the animal upon which experiments are carried out recalls that of plague: congestions adenitis, hypertrophy of the spleen with necrotic infectious nodules which are also noted in the liver. In man, necrotic inflammatory lesions in the primary lesion, the lymph nodes, the liver, the spleen, etc. In semiacute cases epithelioid and Langhans cells may be like those of tuberculosis.

SYMPTOMATOLOGY

Various forms may be distinguished; ulcero-glandular, oculo-glandular, ganglionary, and a generalized form, typhoidal without apparent primary lesion. The general symptoms persist from two to three weeks with abatements: adenopathy may suppurate. The initial ulcer is occasionally very noticeable.

PROGNOSIS

Mortality does not normally exceed 4 per cent. Pulmonary localizations and, above all, meningitis render prognosis rather gloomy. Convalescence is slow.

DIAGNOSIS

The antecedents (skinning of rabbit, bite), the initial cutaneous or conjunctival complex, a fever of long duration, will attract attention. Serology provides a test of agglutination (second, and especially third week) and a cutaneous test. The most satisfactory research of the bacillus is by guinea pig inoculation. It should be noted that this animal may be inoculated transcutaneously as with the plague, but, in this case, the bacillus will not develop on poor culture media. It is also much smaller and more abundant in the lesions.

Treatment: Streptomycin is a powerful curative, with the same dosage as in plague.

Prophylaxis: Consists in the careful handling of suspected animals.

11. MELIOIDOSIS

Definition: An infectious disease resembling glanders and caused by a microbe known as Whitmore's bacillus (1911).

The disease attacks the rodent and is transmitted directly.

GEOGRAPHIC DISTRIBUTION

This disease, which was first observed in Malaya (Whitmore 1911, Stanton 1917), appears to be particularly widespread in the Far East, principally the Indo-Chinese peninsula sensu lato.

ETIOLOGY

The Bacillus of Whitmore strongly resembles that of glanders: a bacillus somewhat polymorphic, mobile, Gram-negative, developing easily, preferably in aerobiosis, liquefying gelatin, pathogenic for most laboratory animals through the skin or respiratory mucus. Like the glanders bacillus, it may, if introduced into the peritoneum, produce orchitis in the guinea pig.

Transmission is probably effected by ingestion, the infected animals eliminating the germs in the urine, the feces, and respiratory emanations. The rat probably plays a part in transmission.

Accidental inoculations of morphia addicts have been noted.

PATHOLOGY

Nodules undergoing casefication may be found in most of the organs, especially the lungs, the spleen, and the liver. Ulcerated and fistular nodules appear on the skin. The bacillus has been found in the blood, the urine, the lesions, and expectoration.

SYMPTOMATOLOGY

The clinical aspect is far from characteristic and clinical diagnosis is rarely etiologic. Cases of a septicemic appearance are found. Others have rather the appearance of pneumonia. Visceral nodules may lead one to consider abscesses arising from any cause—in the case of chronic progress, abscesses of the limbs, attacking the bones and culminating in fistulae. The disease may simulate various conditions.

Prognosis: Death usually ensues.

Diagnosis: Only bacteriology can identify the cause of the symptoms observed.

Treatment: Nothing precise can be indicated.

Prophylaxis: Foodstuffs to be protected against rats.

12. YELLOW FEVER*

Definition: An endemo-epidemic disease caused by a filtrable virus, transmitted in its epidemic forms by *Aedes aegypti,* characterized by fever, jaundice, albuminuria, hemorrhage, a high mortality, and a permanent immunity.

HISTORY

It is possible that yellow fever raged in 1493 in the West Indies among the members of Christopher Columbus' expedition. On the other hand, it is generally thought that the first definite description is that by Lopez de Cogoludo (1649, in Yucatan). Nevertheless, this description, which indicates vomiting with blood, makes no mention of jaundice. Since then many epidemics have been noted in American cities and on the coast of Africa. In 1881 a Cuban doctor, C. Finlay, endeavored to fix the role of the Aedes transmitter. This transmission was established only in 1900–1901 by an American commission sent to Cuba under the order of Reed, and including also Carroll, Agramonte, and Lazear. Their work was later confirmed by Marchoux, Salimbeni, and Simmond in Brazil.

In 1919, Noguchi obscured the question by isolating, in patients allegedly suffering from yellow fever, Leptospires which appeared to be the cause of the disease. Later *Leptospira "icteroides"* was identified with the agent of Weil's disease (L. icterohaemorragiae), and in 1928 Stokes, Bauer, and Hudson on the African coast demonstrated the accuracy of Reed's findings (vide Etiology).

It is fitting that we should remember the scientists who succumbed to the disease in the course of these studies: Lazear died in Cuba at the age of 34; Carroll who, after voluntary infection by mosquito, contracted a disease which, though not fatal, seems to have cut short his life; Stokes, Noguchi, etc. Nor can one forget the volunteers who accepted the risks of the experiments of the first commissions—a few Spanish immigrants and members of the American Army.

GEOGRAPHIC DISTRIBUTION

The original focus of yellow fever is not exactly known. Historical documents on past epidemics, and the fact that an animal virus reservoir is known in tropical America, render this country open to easy suspicion. Nevertheless, the Aedes appear to be originally an African genus and, in any case, it is *Aedes aegypti,* a pantropical insect, which is the epidemic agent of the disease.

Centers known for one or two centuries are as follows:

1. *America:* (a) West Indies and Central America.

(b) The South of the United States with, at times, epidemics in summer as far north as Philadelphia, New York City, Boston. These two centers now appear to have died out since 1900 (Cuba) and 1905 (New Orleans).

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* French: Fièvre Jaune; German: Gelb Fieber.

(c) South America, with epidemics in many of the large cities of Brazil and various Pacific states, and a vast endemic area comprising the greater part of the Amazon basin and neighboring regions.

2. *Europe:* From 1700 to 1821 numerous epidemics are said to have been observed, especially in Spain, and more rarely in Italy and France. It is evident that diagnosis is by no means always certain, but we know that *Aedes aegypti* exist in the Mediterranean areas, and there is, therefore, no reason for doubt in view of the frequent connections between Spain and South America.

In 1865 two small epidemics broke out in Swansea and St. Nazaire on board ships coming from the West Indies, and among individuals connected with the vessels. The St. Nazaire epidemic was truly a summer one (July–August), but that in Swansea appears to have occurred between September 9 and October 4. The temperature was possibly sufficiently high to maintain the Aedes in an active state.

3. *Africa:* The West Coast has experienced many epidemics, from Senegal to the estuary of the Congo (1927 and 1928), but particularly in West Africa. Recently a serious epidemic ravaged the Nuba Mountains (Anglo-Egyptian Soudan). In addition, the existence of protective seric reaction shows a large area of endemicity toward the center of the Continent (a large part of the Congo, Nigeria, Tchad, and the Upper Nile). It is worthy of note that a large part of the distribution area of *A. aegypti* is free from epidemic yellow fever, such as India, the Far East, the Pacific territories and also the East Coast of Africa* and the Islands of the Indian Ocean.

ETIOLOGY

Yellow fever is due to a filtrable virus measuring from 18 to 27 millimicrons. Kept below 0° C. in the refrigerator and in a dry state, it preserves its virulence for years. It is isolated from the blood during the first five days of the disease. Being essentially "viscerotropic" it is subsequently found in the liver, producing there serious necrosis which is frequently fatal. The Asiatic monkey *Macacus rhesus* (Macaca Mulatta) when injected under the skin with this viscerotropic virus will die in less than eight days from acute hepatitis (Stokes, Bauer, and Hudson, 1928). Theiler in 1930 succeeded in inoculating the virus (isolated at Dakar by Sellards in 1928 and called "French strain") intracerebrally in the mouse. After some passages from mouse to mouse the yellow fever virus becomes "neurotropic." Mice die of encephalitis between the fourth and tenth days. When inoculated into the brain of the monkey, this virus, turned neurotropic, produces fatal encephalitis. Injected under the skin of monkey or of man, it produces immunity but no symptoms develop, the virus having lost its viscerotropism. Thus appeared the first possibility of effective vaccination (Sellards and Laigret). As the disease displays a very extensive immunity, the search for antibodies was made possible by protective tests on the mouse, replacing, with advantage, *M. rhesus:*

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* The southern coast of the Red Sea is now considered an endemic zone, in addition to the Barotse and Balovale (N. Rhodesia) to the south of the Congo.

Theiler's intracerebral test on 4 mice or Sawyer's intraperitoneal test after cerebral lesion on 6 mice. A mixture of virus (ground brain of a mouse) and serum is injected. If the latter is positive the mice survive, the virus having been destroyed by the antibodies of the serum.

The yellow fever virus is cultivated on tissues (ground mouse or chicken embryo) or on chorio-allantoid membrane of chicken. Theiler obtained by culture a favorable variation of the Asibi viscerotropic strain (a very virulent strain which killed Noguchi, Stokes and other research workers) isolated from the native, Asibi, who, however, recovered after a very mild yellow fever attack). The virus known as 17 D lost all viscerotropism and could itself be used for vaccination (Lloyd).

The guinea pig is sensitive to the neurotropic virus only when it is introduced intracerebrally. In this case the animal develops a fatal encephalitis. The hedgehog is sensitive to viscerotropic and neurotropic virus and dies of hepatitis or encephalitis (Findlay).

TRANSMISSION

Yellow fever is known in three epidemiologic forms:

1. The epidemic urban type (on two shores of the South Atlantic).
2. The endemo-epidemic rural type (in the interior of South American and African continents).
3. The sylvan type or “jungle yellow fever” (Soper) with vectors other than *Aedes aegypti* (forests in Brazil, possibly in Africa also).

The first two forms are due to transmission by *Aedes aegypti*. This very domestic mosquito rarely leaves the habitations and feeds preferably on man. It is easily recognized by its black and white stripes and a design in the shape of a lyra on its thorax. Only the female bites. Three days after the meal, the eggs are laid separately, at less than 100 meters from habitations, on small collections of water or any damp object, remains of broken pots, bottles, tins, pineapple leaves, sisal, coconut trees, hollow trees, etc. The eggs resist desiccation very well (for six months). It even increases the percentage of the hatchings. The eggs are white at first, then turn black. The larvae are hatched in less than twelve hours in water. After a long spell of drought, a rain shower suffices to bring about almost immediately the hatching of the larvae and a few days later that of the adults.

It takes about a fortnight from the first case of yellow fever to the breaking out of an epidemic. This interval corresponds with the average time of incubation in man (1–6 days), added to the average time of incubation of the Aedes, varying according to the temperature (4–20 days).

The *Aedes aegypti* remains infective during its whole life. The virus multiplies in the mosquito (optimum temperature 26 C.) and the salivary glands are infected. Experimentally the virus has also been found in several species and genera of mosquitos such as *Anopheles, Culex, Eretmopodites, Mansonia,* and *Haemagogus. A. aegypti* is the only mosquito involved in the transmission of epidemic urban yellow fever and the reservoir is purely human in that case. In the rural epidemic form of yellow fever, *A. aegypti* and possibly other vectors are the transmitters and there is a probable animal reservoir. If we keep the strict definition of "jungle yellow fever" as yellow fever in a region without *A. aegypti,* then we must admit that this third form is necessarily transmitted by other insects and possibly Arthropods infected on wild animals. The existence of jungle yellow fever as such has been clearly proved in South America through the isolation of virus in the mosquitoes *Haemagogus capricornii* and *spegazzinii falco,* as well as in certain primates (Laemmert and Ferreira, 1945, in 4 Marmosets, *Callithrix penicillata*). Different species of *Haemagogus* such as *equinus, splendens* and different *Aedes* transmit the disease at least experimentally and most probably naturally. On the other hand protective sera are commonly found in South American marsupials (*Caluromys* and *Metachirus* opossums) and primates (*Callicebus, Cebus, Saimiri, Aotus,* and several species of Marmosets). All monkeys, however, are not equally important in the maintenance of virus cycles in nature, some of them having, even in experimental infections, not enough circulating virus to infect *Haemagogus* mosquitoes (Bates and Roca Garcia 1946, Waddell and Taylor 1946). The South American animal reservoir seems to be exclusively arboreal. *Haemagogus* also prefers to live above ground level (Boshell). From this fact emanates the hypothesis that isolated cases of minor human epidemics frequently observed in Brazil after the cutting of trees in the forest might be caused by the bite of mosquitoes brought to the ground on that occasion. In Africa, yellow fever virus has been found in *Aedes simpsoni* in the Bwamba region near the Semliki valley between Uganda and the Belgian Congo. *A. aegypti* is not absent from that region nor, apparently, from any part of central Africa. In the Bwamba region, however, *A. aegypti* plays no important role in the epidemiology. The name of "forest yellow fever" has been used, therefore, rather than the restricted one of "jungle yellow fever" (Smithburn and Haddow, 1946). The African forest fever and the American jungle fever may be basically similar. For instance, in the Bwamba region 61 per cent of the monkeys show a positive protection test. This is found as well in Papio monkeys which spend most of the daytime on ground, as in Colobus, Cercocebus, and Cercopithecus, which descend to the ground only for short periods. *Cercopithecus nictitans,* however, is a notorious raider of plantations and may act as a link between the forest and the human endemic disease. The African forest vector might be *Aedes africanus* which is active and almost exclusively found in the forest canopy between sunset and sunrise, at which time both arboreal and terrestrial monkeys are in the tree tops. The human host in the African forest type of fever probably acquires infection by entering the forest, as in Colombia, and being bitten by the forest vector or through a semidomestic vector such as *A. simpsoni*, infected on the edge of the forest by some monkeys.

PATHOLOGY

The viscerotrope virus of the disease produces an extraordinarily acute septicemia,* since 1.10^{8} cc. of blood of Macacus rhesus has been sufficient to cause infection. This condition is accompanied by very serious alteration in various organs, particularly the liver, and to a lesser degree the kidneys, the heart, etc.

Macroscopically one finds jaundice, ecchymoses, traces of hemorrhage either in the primary duct or in the stomach (hemorrhagic aspect at the apex of the folds) or, more rarely, in the intestine. The liver is sometimes congested, sometimes of a yellowish color (fatty degeneration). Necrotic deterioration of the parenchyma is commonly very noticeable under the microscope.

Histology is particularly interesting and informative in the liver which displays a combination of fatty degeneration (reversible lesion) and disseminated necrosis. The latter is, in the most typical cases, situated in the middle zone of the lobule, the two centrolobular and peri-portal zones especially displaying fatty degeneration (Rocha Lima). The most heavily attacked cells undergo a necrosis, changing the cytoplasm into an acidophilic block in which may often be observed small lipoidic vacuoles, and in which the nucleus has completely, or almost completely, disappeared. These are the bodies of Councilman which, on slight enlargement, appear in pink (eosin) on the preparation (avoid confusion with the red globules accumulated here and there in a sinusoid).

The nuclei of hepatic cells which are not too far degenerated may display (man, monkey), in some 25 per cent of cases, granular acidophilic and intranuclear inclusions (Torrès bodies).

Neither Councilman bodies (which may be found in cases of burns treated with tannin, in cases of intoxication by CCl_4), nor Torrès bodies (which are found in the lesions of Rift Valley fever) are entirely specific. But the abundance of the first bodies, the intense fatty degeneration, the scarcity of cellular infiltration are significant. The Rocha-Lima type of distribution, though very important, is nevertheless neither specific nor constant.

The kidneys display degeneration of the tubuli and calcic cylinders (moderate nephrosis). The myocard shows either waxy or fatty degeneration. A certain degree of cerebral perivascular infiltration is also noted.

It may be supposed that among patients who survive, and there is an extensive range of gravity, the lesions remain of a reversive type without necrosis.

SYMPTOMATOLOGY

The period of incubation is from three to six days, and the onset frequently acute. The observations of Lazear should be remembered: He was bitten on September 13, 1900, by a mosquito; on September 18 he felt unwell, had a first shivering attack at 20 hours, a second at 22 hours; on the nineteenth at 12 hours his temperature was 39 C., pulse 112, his eyes bloodshot, the face red; at 18 hours, temperature reached 40 C., pulse 106, isolation. The sickness became progressively worse during three days and the young scientist died on September 25 after having had "black vomit." With Carroll, voluntary infection by mosquito saw an incubation period of four days.

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*Insofar as this term may be applied to viruses which we know to be generally intracellular bodies.

Clinical evolution may, in certain cases, be asymptomatic or, again, resemble some slight ordinary fever.

Let us recall that the Asibi strain, which is very virulent and the cause of numerous fatal contaminations in the laboratory, was isolated from the Negro Asibi, who was attacked by a quite insignificant ambulatory fever.

These abortive cases, perhaps the most numerous if one is to judge from the frequency of protective tests, have been defined with equal success both clinically (former observations) and by the isolation of the virus. The classic yellow fever, on the other hand, appears with striking phenomena which it is convenient to classify in two periods:

1. Septicemic period: The virus is abundant in the blood with infectiousness at a maximum, persisting about three days. This is the period of purely infectious phenomena: fever with moderately or very sudden onset, reaching 40 C. from the second day, with acute discomfort: headache, rachialgia, congestion of the face and eyes, rapid pulse. Slight albuminuria may be observed about the thirty-sixth hour. Fever persists with, frequently, a tendency to drop toward the fourth day, this drop leading sometimes to a cure, and sometimes to a new increase in the temperature, introducing the signs of the succeeding period:

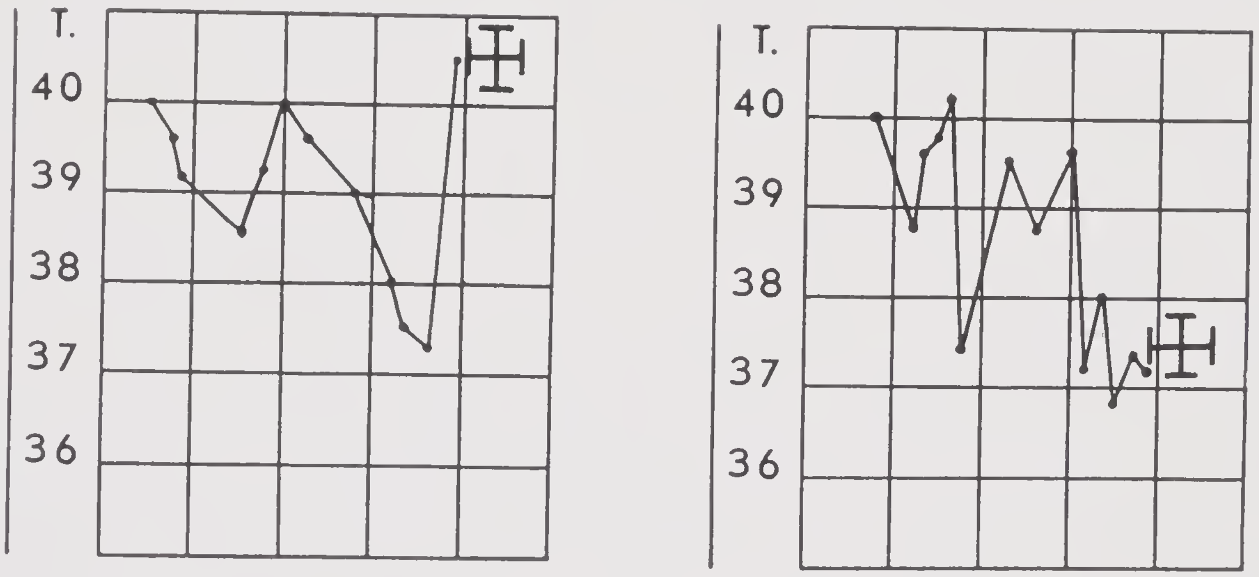

Chart 18. Two fatal cases of yellow fever (Dr. Mouchet, Congo)

2. Period of organic deterioration: Albuminuria becomes pronounced with cylinders, tendency to anuria. Jaundice makes its appearance and the epigastric region becomes more sensitive, vomiting more accentuated. On the other hand, icterus may be totally absent. The tendency to hemorrhage

becomes evident: ecchymoses, frequent hemorrhage, and, above all, "black vomit," vomiting of blood like coffee-grounds, sometimes also melena. The weakness, always considerable, becomes worse, the pulse becomes relatively slow (Faget's sign). The mind frequently remains clear, the collapsus and the anuria are fatal to the patient whose anxiety is often very marked. Convalescence has no noteworthy features, and relapses are rare.

PROGNOSIS

An acute illness in which the majority of patients are either dead or on the way to recovery toward the tenth day. The prognosis has always been considered as very serious, the average fatality being estimated at 50 to 60 per cent. But, taking into account benign cases, frequently not diagnosed, the lethal character of the disease is difficult to determine. It has been asserted that the benign cases occurred most frequently among children, but this concept should not be carried too far. Incoagulable blood, disappearance of the complement, persistent leukopenia, and oliguria are bad omens.

DIAGNOSIS

This is difficult during the initial period. One may consider various serious diseases and, naturally in hot countries, particularly malaria. The negativity of the blood, the early and progressive albuminuria distinguish yellow fever from malaria. Other diseases are eliminated by their peculiar signs: severe influenza (frequent catarrhal signs), plague (bubos), etc. Leukopenia and albuminuria tend toward yellow fever. The urine may also contain peptones, but no hemoglobin, which would eliminate the diagnosis of blackwater fever.

During the second period, the differential diagnosis may be done with various infectious icteri: benign epidemic hepatitis rarely leads to confusion (slightly or not at all febrile, slow evolution, discoloration of the feces). Malignant hepatitis is fairly rare and displays hepatic atrophy, either coma or excitement, severe icterus and a late preagonic fever. Bilious malaria has its blood signs. Toxic jaundice is but slightly or not at all febrile.

Leptospirosis may lead to confusion, and the classic example of Noguchi must encourage caution. This disease, described by Weil in 1886, has an incubation period of longer duration (5–14 days), distinctive etiologic characteristics (contact with water polluted by rat urine), a fever of longer evolution (two weeks). Icterus without discoloration appears toward the fourth day and may, indeed, be entirely absent. Oliguric or hemorrhagic nephritis, or a hemorrhagic syndrome may occur. Myalgia in the calf, signs of meningitis, late iritis are peculiar to Leptospirosis. The laboratory findings will be decisive. The leptospiroses may be isolated in the blood during the first week, in the urine during the second, this most successfully by inoculation of young guinea pigs with centrifugal residue. Toward the end of the illness and in convalescence, the serum displays agglutinous and lytic properties in relation to the leptospires. These parasites produce leukocytosis, whereas yellow fever virus develops leukopenia.

Laboratory diagnosis of yellow fever is based on:

1. Isolation of the virus in the Macacus or the mouse, with immunity test by a known protective serum.

2. On the histology of the liver, fixation with 10 per cent formol on the body. To avoid the necessity of an autopsy the so-called viscerotomic trocar may be utilized.

3. The verification during convalescence of a protective power in the serum. It is clearly desirable to ascertain the results obtained from serum taken at the onset of the disease. That is a general rule particularly important in countries with a high yellow fever endemicity.

TREATMENT

The treatment is purely symptomatic: absolute rest, plenty of liquids and particularly glucose, alkalines, citrus juice, calcitherapy (excess of guanidine in the blood). The convalescent serum so far has not shown its activity. During convalescence a diet rich in carbohydrates and poor in fats, milky foods, eggs, and vitamins is advised.

PROPHYLAXIS

Yellow fever is limited to South America and Africa. The *Aedes aegypti* being common in the whole intertropical zone, it is extremely important to apply sanitary measures to avoid the spread of the yellow fever endemic. Most of these measures have been decreed by international conventions.

1. Human reservoir of virus: Through the protection test in the mouse, the distribution of yellow fever has been delimited with precision. It is even possible to establish approximately the age of yellow fever in a region by searching the antibodies in separate classes of age. In the Congo alone, over 10,000 protection tests on mice have been carried out (van den Berghe, Liégois). The organization of a viscerotomy service and the examination of the liver in all cases where death occurred after an infectious illness of a few days allow the discovery of sporadic cases of yellow fever and ascertain the existence of suspected foci. Finally, only nonfebrile persons and those recently vaccinated are permitted to leave endemic territories.

2. Transmitter: The struggle against the larvae is imposed at all the posts and all the centers which are in the endemic zone. It is based on the

survey of the innumerable collections of water, down to the very smallest, which are found around the human habitat. Very strict control is exacted at all the airports and the airplanes leaving the endemic region for continents free from fevers are disinfected. For this purpose pyrethrum or DDT aerosol bombs are mostly used (see prophylaxis of malaria).

3. Healthy man: It would be desirable if the entire population of the endemic zone could be vaccinated. Vaccination is obligatory for everybody going to South America and Africa.

There are two types of vaccine which are at the present moment considered efficacious. (1) Virus 17D cultured on chick embryo (vaccine according to Lloyd). A subcutaneous injection guarantees protection as demonstrated by the test on the mouse in at least 50 per cent of the cases. (2) The "French strain" neurotropic virus (vaccine according to Peltier and colleagues. The virus of the mouse is scarified at the same time as the smallpox virus. This constitutes a very easy to apply mixed vaccination. Millions of individuals have been vaccinated in French Africa by this method. Yellow fever protection is demonstrable in close to 100 per cent of the cases.

During an epidemic particularly severe measures must be taken in urban agglomerations.

1. Human reservoir of virus: The agglomerations affected by the epidemic must be encircled by a sanitary cordon. The yellow fever patients are placed in beds, under mosquito nets. The house which shelters them will then be closed and all mosquitoes inside it killed.

All ships arriving from a suspected or affected port during a time of epidemic must submit to a quarantine of six days at 200 meters distance from shore and vaccinations must be applied to all persons on board.

2. Transmitter: The anti-Aedes campaign must be taken up in the entire agglomeration, not merely against the larvae, but also against the adults. The DDT house-spraying is particularly efficacious against the *Aedes aegypti* because of the domestic habits of this mosquito. (See prophylaxis of malaria).

3. Healthy man: The whole population must be vaccinated. The use of mosquito nets is indispensable, as soon as night falls.

13. DENGUE

Definition: Dengue* is an epidemic disease caused by a filtrable virus transmitted by *Aedes aegypti*, clinically characterized by a short period of fever and by a mild evolution.

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* The etymology of the word dengue is uncertain. Denguero in Spanish means "dandy" alluding to the affected and stilted gait of the dengue patients suffering from algias.

GEOGRAPHIC DISTRIBUTION

The disease is prevalent in all the hot zones which are the habitat of the *Aedes aegypti*. In Europe, particularly the eastern part of the Mediterranean (Athens, 1928); tropical and subtropical America, including the South of the U.S.A.; Asia: Syria, etc.; in Oceania: the Philippines, Australia, the Pacific Islands; Africa: Egypt, French West Africa, the Congo.

ETIOLOGY

Filtrable virus present in the blood of the patient during the first 90 hours. No animals being available for experiment (monkeys are only imperfectly receptive) the experimentation of this virus has been delayed. The culture is possible on the chorio-allantoid membrane of the chick embryo (Shortt).

TRANSMISSION

Essentially by *Aedes aegypti* (Ashburn and Craig, 1907, in the Philippines) which becomes infectious about ten days after the infecting meal and remains so for its entire life. *Aedes scutellaris* is a transmitter in New Guinea (Fairley, 1945). Nothing is definitely known regarding the reservoir of virus which is probably human.

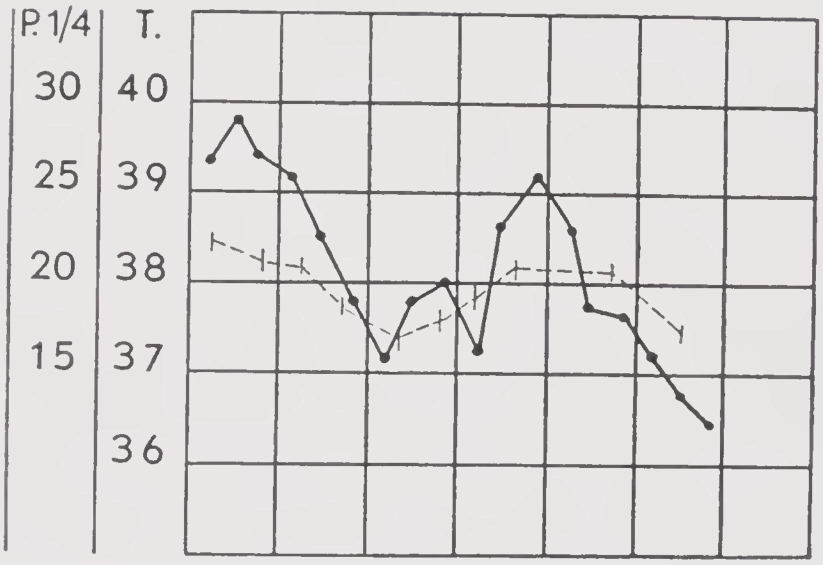

CHART 19. Dengue fever

PATHOLOGY

The disease being mild, there is little documentation on its pathology. The virus seems to produce alterations in the capillaries and the parenchymes. Death is generally the result of old age or of complications.

SYMPTOMATOLOGY

The descriptions given in various countries do not always bear comparison.

The incubation takes two to nine days. The onset is most often very sudden: high fever and various malaises, particularly algias, in the eyeballs, head, spinal column, limbs, general prostration.

The fever lasts six to seven days with sometimes an abatement toward the third or fourth day giving a saddle-form curve. Toward the end of the fever period, sometimes earlier, exanthema appears. It spreads over the neck, the upper part of the chest, hands and feet, the limbs and the face. Its appearance is sometimes roseoliform, at other times morbilliform or scarlatiniform and it vanishes in two or three days with a slight desquamation. Rather often, exanthema is not noticeable.

An early facial exanthema is also mentioned which recalls solar erythema with conjunctival and pharingeal hyperemia. One should point out the cervical adenopathy, digestive troubles, and slight albuminuria. The pulse, very rapid at the beginning, sometimes manifests later a relative bradycardia with low tension.

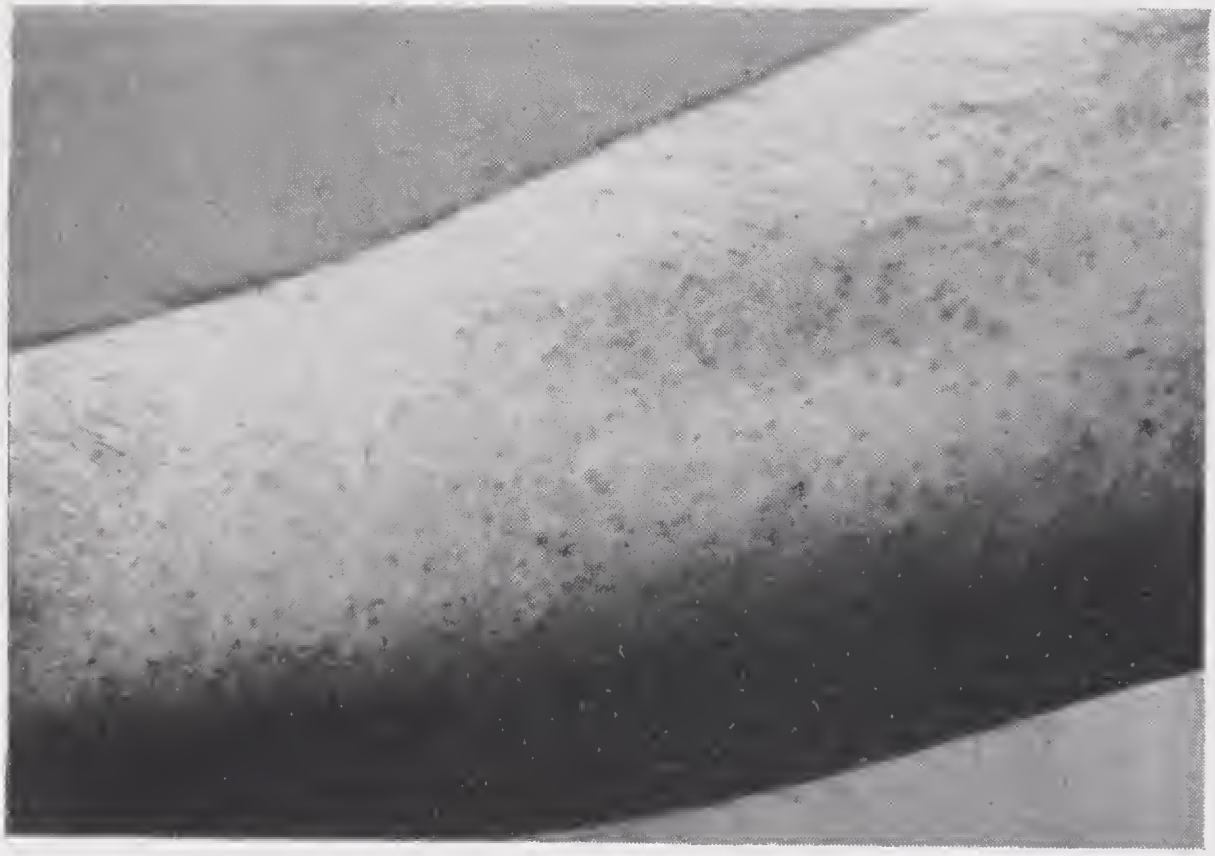

FIG. 40. DENGUE
Experimental infection on the ninth, ill on thirteenth, photography on the nineteenth (courtesy Dr. E. P. Snijders, Indisch Instituut, Amsterdam)

According to investigations made at Bangui (French Equatorial Africa), cephalalgia, bradycardia, the stiffness of the neck, and the rachialgia are said to be of meningitic origin. The cerebrospinal fluid is always under tension and would give a very light cytochemical reaction.

Complications: Certain epidemics show vomiting, diarrhea tinged with blood, parotiditis, orchitis, petechias, and nervous troubles. Convalescence is often very troublesome, while furunculosis and pyodermatitis are often seen.

Prognosis: Always favorable. Nevertheless, due to various complications, the death rate reaches 1.5 per thousand.

DIAGNOSIS

The symptomatic triad is: intense fever with eventually a saddle curve, algias, and a late exanthema. Unfortunately there are many atypical cases and even epidemics. In endemic dengue there is seldom any trace of a saddle curve (partial immunity).

Clear laboratory signs do not exist. One should mention, however, a notable neutropenia with leukopenia.

A differential diagnosis must take a series of diseases into consideration.

1. *Influenza:* Respiratory complications, absence of eruptions, tachycardia, and an almost normal hemogram, are symptoms typical of influenza.

2. *Yellow Fever:* Considerable albuminuria, jaundice, gravity.

3. *Mud Fever:* A disease of influenza-like appearance in which it is possible to demonstrate leptospiras (*L. grippo-typhosa*).

4. *Red Congo Fever*

Described in Central Africa, this disease manifests a slight fever of short duration, an ordinary early exanthema of variable appearance (most often morbilliform), adenopathy, blood lymphocytosis without leukopenia, and very few algias.

The identification of this disease is very uncertain. The closest resemblance is dengue. Jadin has recently (1944) shown that in certain of his patients the Rickettsias of murine typhus could be isolated. It has not been proved that all the cases of red fever belong to the Rickettsial diseases and other observers in the Congo have not been able to confirm these results. Jadin notes slight reactions of Weil-Felix and these rather with OX K.

5. *Five Day Fever*

Mild fevers of five days (van der Scheer), of six, seven, and nine days have been described, which all seem to belong to the endemic dengue. Transmission has been achieved with all of them in Amsterdam through mosquitoes. They might eventually be due to closely related viruses (Indonesia, Calcutta, Panama).

6. *Rift Valley Fever*

Man may become affected by this virus disease of sheep. The disease resembles dengue but is due to a different virus. A protection test allows a retrospective diagnosis.

7. *Colorado Tick Fever*

The clinic, hematology, and size of the virus are very like dengue. Nevertheless, experiments made on volunteers (1946) have shown distinct immunologic characteristics and, in addition, Colorado tick fever produces no eruption. The disease is also distinct from Bullis fever. Experimentally, Colorado tick fever is transmissible to the Syrian hamster.

8. *Bwamba Fever*

This disease has been isolated in Uganda in 1941 by Smithburn, Mahaffy, and Paul. It is characterized by a sudden onset with fever lasting five to seven days, algias, and a mild prognosis. Several strains of virus have been isolated in mice after intracerebral or intranasal inoculations. These strains do not give cross immunity with yellow fever. Other viruses, antigenically different, have also been isolated by the same authors in the Bwamba region.

Acute Articular Rheumatism: A disease which is seldom epidemic and which prevails especially in cold countries with noticeable anemia, true arthritis, instead of the algias of dengue, antecedents of angina, endocarditis, and favorable therapeutic response to salycilate.

Treatment: The treatment is purely symptomatic, keeping the patient under observation during convalescence. The vacuating lumbar puncture is thought to possess excellent therapeutic value.

Prophylaxis: Reduced to the isolation of the patient for at least three days under mosquito nets and to the fight against Aedes (see section on Yellow Fever). No efficacious method of vaccination has been suggested.

14. SAND-FLY FEVER*

Definition: Febrile epidemic disease due to a filtrable virus, transmitted through the bite of Phlebotomes, and with a rapid and favorable evolution.

GEOGRAPHIC DISTRIBUTION

First studied in Dalmatia, this disease has been found practically everywhere in the Mediterranean region as well as in Asia, America, East Africa, etc. There is no proof of its having occurred in Central Africa.

ETIOLOGY

The works of Doerr, Franz, and Taussig (1909) have shown the existence of a virus that circulates in the blood during the first thirty-six hours of the illness. It is possible to inoculate it experimentally into man. The diameter of the virus is about 160 millimicrons.

There is no susceptible laboratory animal. The culture of the virus has proved successful on chorio-allantoid of chick embryo (Shortt, 1936).

TRANSMISSION

The Phlebotomus which has bitten a sick person becomes infectious about a week this meal. *P. papatasii* is a transmitter in the Balkans and *P. minutus* in Aden. The virus reservoir seems to be human.

SYMPTOMATOLOGY

Incubation takes from three to nine days, according to observers in Dalmatia. It is from two and a half to six days in 95 per cent of the experimental subjects (Sabin and colleagues). The onset is sudden with fever and shivers. The temperature rapidly rises to 39–40 C. and falls to normal about the third day, sometimes in crisis. The duration of the fever varies between less than one day and nine days persisting from two to four days in 85 per cent of the patients. Recurrences have sometimes been observed. Various algias are very pronounced: eyeballs, head, rachis, different muscles and nerves. Stiffness of the back of the neck sometimes occurs. The face and the conjunctiva are red, the conjunctival redness spreading out in a horizontal band. The pharynx is also congested. Gastrointestinal disturbances are very marked. The spleen and liver do not show any symptoms. As regards the circulation, a rather serious bradycardia, which sometimes proves persistent, is observed. The blood exhibits leukopenia. There is generally no exanthema.

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* French : Fièvre des Trois Jours (à Pappataci); German: Pappataci Fieber.

According to observations made in Diego-Suarez, the cerebrospinal fluid, in addition to clinical meningal signs, shows a slight lymphocytosis combined with a strong albuminosis. These facts have not been confirmed by Sabin and colleagues (five lumbar punctures).

The evolution, as indicated by the French name for the disease, is very rapid.

Prognosis: Favorable in spite of the grave picture at the beginning and the sometimes prolonged convalescence. In military circles it constitutes an important cause of temporary invalidization.

Diagnosis: Sand-fly fever is very difficult to diagnose. One has to take into account (1) the epidemiology (hot season, insects); (2) the bradycardia; (3) the leukopenia, at any rate after the first days and during apyrexia with lymphocytosis and a shift of the hemogram to the left.

Dengue generally has a longer period of fever (5–7 days in 80 per cent of the patients), adenopathy and frequently exanthema.

Treatment is purely symptomatic.

Prophylaxis: This is limited to the protection against the bites of the Phlebotomes and their destruction (see section on Leishmaniasis).

Chapter V

INTESTINAL DISEASES

We believe it necessary to describe rapidly Bacillary Dysentery which, although cosmopolitan in nature, is particularly severe in all tropical countries.

1. BACILLARY DYSENTERY*

Definition: Bacillary dysentery is an endemo-epidemic infection of the intestinal tract caused by the various germs of the genus Shigella. It is characterized by lesions in the intestine resembling those of enterocolitis and causing muco-sanguinous stools, and a greater or lesser degree of toxicity and dehydration.

HISTORY

Bacillary dysentery has been known clinically for a very long time. It has been especially prevalent during military campaigns, when it was always a dreaded plague, even in the last two great wars. The discovery of the bacilli causing the various types of the disease was made by Shiga (1893), Kruse (1900), Flexner, Strong and Musgrave (1900).

GEOGRAPHIC DISTRIBUTION

Bacillary dysentery is a cosmopolitan infection which is, however, more frequent in the majority of tropical countries, no doubt because of insufficient hygiene and the abundance of flies. In the Congo, it appears that the malady was introduced after the war of 1914–1918 and since that time has caused numerous and grave epidemics. Japan, India, the Balkan countries, the Philippine Islands and other islands of the Pacific have also had epidemics. In the temperate countries the infection is especially severe in the summer and autumn seasons.

ETIOLOGY

The Shigella bacilli are Gram-negative, immobile rods, aerobic on ordinary culture mediums and possessing moderate resistance in the external surroundings. They do not attack lactose (except the Sonne type which attacks lactose slowly) and do not produce gas with the sugars. The antigenic and biochemical classification of Shigella is complex. It is possible to distinguish:

1. *Shigella dysenteriae* (type Shiga), which is strongly toxic and does not acidify mannitol or produce indol.
2. *Shigella ambigua* (type Schmitz) which does not acidify mannitol.

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* French: Dysenterie bacillaire; German: Bacillenruhr.

3. *Shigella paradysenteriae:* (types Flexner-Boyd, etc.) which are less toxic, acidify mannitol, and produce indol.
4. *Shigella sonnei* (type Sonne) acidifies lactose slowly.

The significance of these germs is established by their systematic isolation, the existence of their individual toxins, their agglutinating properties (often discrete) in the serum of the patient, and last but not least, of a certain number of positive inocculations, voluntary or involuntary. It is not practicable to separate the various cultures of *Sh. paradysenteriae* in ordinary practice, neither by the test of their agglutinins nor by the sugar tests.

EPIDEMIOLOGY

The reservoir of the virus appears to be purely human: carried by patients acutely or chronically ill, convalescent carriers, or healthy carriers. The transmission is similar to that of typhoid fever: contamination by contact with sick persons, who inevitably soil themselves.

Water, and the foods contaminated by water, also play a great role because of the resistance of the germs which may in certain cases remain virulent for as long as three weeks. The flies also play a notable role, as epidemiologic observations attest (India, Mesopotamia, Balkan countries), as well as the bacilli found within flies captured in endemic areas of the disease.

One recognizes the importance of hygiene, of housing, and of the level of education, etc., in the epidemiology. It is also the cause of persistence of the endemic cases (often caused by *Sh. Sonnei*) in the asylums, prisons, etc. An epidemic is, curiously enough, rarely caused by a single type of Shigella.

Immunity is not negligible.

PATHOGENESIS AND PATHOLOGY

Although the bacilli paradysenteriae have occasionally been found in lymph ganglia, the spleen, and the blood, one can say that Shigella are specifically intestinal germs. owever, their toxins diffuse and create various intestinal or general disorders.

Sh. dysenteriae has an exotoxin mainly, neurotropic, precipitable by trichloracetic acid and an enterotropic endotoxin of a glucido-lipidic nature representing the antigen "O" of the germ (Boivin-Mesrobeanu).

The bacilli paradysenteriae are less toxic and cause fewer extra-intestinal lesions or chronic lesions. Superimposed infections are also observed (coli, etc.). The intestine is the principal site of infection: terminal ileum and the colon in its entirety. The light cases or early cases show catarrhal inflammation, hyperemia and a muco-sanguinous exudation. In the more advanced stage, one observes on the top of the folds of the mucous membrane of the intestine, a diphtheroid exudative membrane, which when it is detached, leaves a very superficially eroded surface. Submucous edema develops and the superficially eroded surfaces are surrounded by a hyperemic area. The cellular infiltration is definite: the mononuclear cells predominate in the wall of the lesion, the polynuclear cells are numerous in the stools. The secondary infections may cause the ulceration to deepen. Cicatrization with hyperplastic regeneration of the mucosa deforms the intestine. This may terminate (rarely) in perforation, in the formation of glandular cysts, chronic ulcerative colitis, by parietal abscess formation or stenosis.

The lesions of the heart, the nerves and the nervous system, and of the joints are of toxic or anaphylactic origin and are not specific. The adrenal glands are also sometimes affected.

SYMPTOMATOLOGY

Incubation is two to eight days. The onset is very variable, sometimes beginning with a mild diarrhea or general digestive symptoms. On the contrary, it may begin with a very severe diarrhea, accompanied by pain and severe general symptoms. The stools, often fecal at first, become muco-sanguinous and finally assume a purulent aspect; exceptionally, they become gangrenous with a putrefactive odor. In certain typical cases, the feces have a spermatic odor; the cultures of Shigella present the same odor. The evacuations are numerous, accompanied by colic cramps and tenesmus, which is sometimes exceedingly painful.

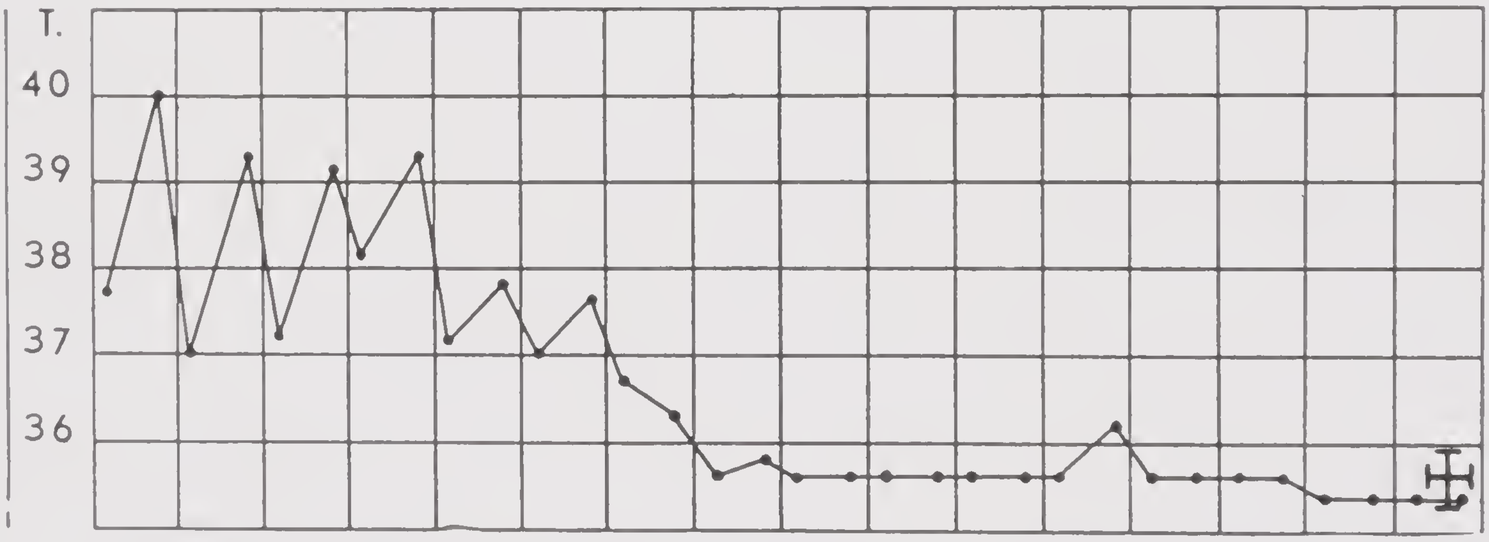

Chart 20. Fatal case of bacillary dysentery (Dr. Mouchet, Katanga)

The general state of the onset is frequently febrile, either a moderate, or more rarely an elevated, fever which lasts only a few days; malaise; sometimes emesis, especially in infants. An elevated temperature does not necessarily mean a bad prognosis. The pulse is almost normal in the light case but can become very feeble in the severe case. Finally, the signs of dehydration are observed in the most severe cases: the skin loses its elasticity, becomes cold, the mouth becomes very dry, etc. The examination shows an abdominal retraction and tenderness on palpation of the colon. Sometimes anal complications such as fissures and prolapsus are seen. The sensorium is nearly normal, although one frequently sees insomnia and, in serious cases, agitation.

EVOLUTION

The progress of the illness is often rapid: in the light cases the duration is only four to five days. The recovery can be relatively easy. In the more serious cases the illness may progress fatally to dehydration and collapsus. At other times the diarrhea may become chronic. The most frequent complications are: secondary infections or arthritis (due it seems to an anaphylactic reaction to the toxins or even to the serum), myocarditis, neuritis, irido-cyclitis, etc. An oculo-urethral syndrome accompanying the arthritis has been described.* This arthritis attacks chiefly the knees and the ankles. The exudate is commonly sterile but is usually found to agglutinate the Shigella.

About 5 per cent of the cases go into the chronic stage and the prognosis is very grave. The mortality is extremely variable. In the literature one finds figures varying between 3 per cent and 25 per cent. Hiccoughs, persistent vomitus, the gangrenous character of the stools, circulatory weakness, motor agitation, subnormal temperature are bad prognostic signs. The dysentery due to Sonne's bacillus is hardly different from the one preceding. Rather severe, even mortal for children, it takes a more benign course in adults, sometimes only simple diarrhea with or without fever.

DIAGNOSIS

The clinical diagnosis is fairly easy in acute epidemic cases which show muco-sanguinous stools, fever and toxic malaise.

The onset is more acute and more febrile than amebiasis which is rarely epidemic (examination shows absence of the amoeba).

The clinical diagnosis in isolated or in benign and chronic cases is difficult. Some cases could easily be confused with gastroenteritis due to Salmonella infection and can be distinguished only by laboratory tests and by the epidemiology (food poisoning).

Bacillary dysentery can complicate other chronic ailments which must be diagnosed. Pernicious malaria can simulate it. The sigmoidoscope may disclose a characteristic state: generalized hyperemia, an excess of mucus, superficial ulcerations or granulations, glandular tapioca-like cysts. The same method can also facilitate isolation of bacteria.

Laboratory Diagnosis: At first this has a negative aspect: eliminate the amebiasis, schistosomiasis, etc., and it has a positive aspect: the presence of Shigella may be discovered by bacteriologic examination, or the presence of a characteristic exudate by histologic examination.

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*Reiter's syndrome (urethritis, conjunctivitis, arthritis, fever) has an obscure etiology, possibly belonging to virus diseases. It affects principally young masculine adults.

Bacteriological Examination: The coproculture. This is the only sure method of bacteriologic examination.

It is absolutely necessary to use fresh stools and if possible, muco-sanguinous material or bloody flakes present in the fecal material. Conservation in an icebox or dilution with two parts of the following liquids often prolong the vitality of the germs in the stools: water, 7 cc.; glycerin, 30 cc. Adjust this solution to a pH of 8.0 with sodium diphosphate to which add a trace of phenol red.

To isolate Shigella, one uses the property which is its peculiar characteristic, i.e., of not turning the indicators in the presence of lactose: lactose agar litmus paper, Endo's medium, Bacto SS Agar, and preferably the highly selective desoxycholate media with or without citrate. In this latter, Flexner bacilli prefer the media with citrate, and the other bacilli without citrate.

The suspicious colonies (after sixteen hours of growth) are submitted to a microagglutination test and another part is isolated and tested in the presence of the various sugars. A further test of macroagglutination will conclude the laboratory identification.

Sero-agglutination is also possible as a means of diagnosis. However, it usually comes too late for clinical purposes and has, therefore, only an epidemiologic interest. In addition, sero-agglutination is less positive in this case than with the Salmonella infections. An agglutination of 1:50 with the Shiga type, of 1:00 with the Sonne type, and 1:200 with the Paradysenteriae type should be strongly suspicious. Higher titers are frequently observed.

It is necessary to put the serum of the patient in contact with various strains of bacilli (one of Shiga, two or three of the Paradysenteriae bacilli, one of Sonne. Ambigua, etc.). The agglutinins appear around the sixth day and disappear after three months.

The bacteriologic methods are not always accessible to colonial practice. They always have the fault either of coming too late (agglutination tests) or of being too slow. The isolation and diagnosis of a germ take at least 24–48 hours and it is these first hours of disease that count the most in the treatment. The importance of cytologic methods of differentiation has, therefore, been insisted on (Anderson, Haughwout, etc.).

Cytologic Examination of the Feces: Fresh examination of the feces, as such, or with the addition of Lugol's solution will eliminate the Protozoa and various worms. Cytologic examination is done with stained preparations. Ash and Spitz advise the following technic:

1. Thin smears of a muco-sanguinous part of the exudate found in the feces, fixed immediately by immersion in hot Schaudin's solution for five minutes.
2. Rinse in water.
3. Three minutes in 50° alcohol.
4. Five minutes in 70° alcohol, with iodine (Port wine color).
5. Ten minutes in 70° alcohol.
6. Three minutes in 50° alcohol.
7. Three minutes in distilled water.
8. Stain in Delafield's ammonium-alum hematoxylin, usually 10 minutes, but it is better to verify it by placing a cover glass on the moist preparation (one can differentiate by acid alcohol), utilizing Eosin as a counterstain. Mount it with alcohol

and balsam. The following is an outline of the principal differences between the two important dysentery groups:

	Bacillary Dysentery		Amebic Dysentery		
		per cent		*per cent*	
Neutrophils	+++	91	+	7.5	(x)*
Eosinophils	0	0.01	+	3.2	(xx)*
Macrophages	++	1.8	0		
Lymphocytes	+	2.8	+	2.5	(xxx)*
Mononuclears	+	1.61	+	0.7	
Plasmocytes	+	1.6	+	1.8	
Erythrocytes	++	discrete	+++	(in clumps)	
Epithelial cells	+	1.5	+	1.3	
Alterations					
Ghost cells (x) and Ring nuclei (xx)			Nucleated pyknotic bodies cytoplasms partially lysed (83 per cent) (xxx)		
Crystals of Charcot Leyden	0		+		
Bacteria	0		+		
Protozoa	0		Entameba (vesicular nucleus)		
Fibrin	++		—		
Mucus	++		+		

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* (x) Ghost cells: macrophages in a state of lysis, having a vague appearance.
(xx) Ring nuclei: Polymorphs whose nuclear contours are very distinct.
(xxx) Nuclear masses, with hardly any remaining cytoplasm.

One must not lose sight of the possibilities of a mixed infection, such as amebic and shigella infections together.

The use of Emetine as trial treatment must be rejected. This alkaloid can aggravate the condition of a patient in a toxic stage of bacillary dysentery.

The diagnosis of chronic cases is difficult. It is necessary to look for the bacilli even at the site of the ulcers (rectoscope), eliminate colitis from other causes, take x-rays of the patient which can very usefully show the state of the intestine. The rectoscope, difficult to use in acute conditions, can be very useful in the diagnosis of chronic cases (see Amebiasis).

TREATMENT

The introduction of the sulfonamides has changed the treatment of bacillary dysentery and it is only in the case of a positive diagnosis of *Shigella dysenteriae* (Shiga) that one should associate serum with the chemical treatment. Of considerable value are the sulfonamides which are poorly absorbed in the intestine, although sulfadiazine appears superior (or sulfathiazol in the case of Sonne).

Sulfaguanidine: In the acute case: 3.5 Gm. every four hours both night and day, until a reduction in the number of stools is obtained (not more than 3–4 a day). One then gives the same dose every eight hours until the normal state is obtained for 3–4 days. If one does not obtain this effect in a few days (5–6 days), it is best to try the other methods of treatment. Up to 110–180 Gm. of sulfaguanidine has been given in this type of treatment.

Chronic Cases: Three to 5 Gm. of sulfaguanadine every eight hours for 1–2 weeks.

Sulfasuccinyl (para-succinyl-amido-benzene-sulfonamidothiazol) is even less absorbable than sulfaguanidine (5 per cent of the dose taken) and is thus very slightly toxic. The dose consists of 3 Gm. every four hours, and later every six hours.

Phtalyl-sulfathiazol: This is likewise only slightly absorbable and is twice as bacteriostatic as the preceding drug.

In cases in which sulfaguanidine cannot be used, it is best to resort to sulfathiazol, or, better yet to sulfadiazine: 2 to 4 Gm. as the initial dose, then 1 Gm. every four hours. It is necessary to observe the urine output which should be at least 1500 cc. per day, and to prescribe alkalines.

Other Treatments: Anti-Shiga serum is available, and in case the definite bacteria have not been isolated, the polyvalent serums can be used in the toxic cases. It is necessary to utilize the large dosages (10,000 units) and to repeat the dose a second time during the day if the subject is not hypersensitive. It is best always to make a hypersensitivity test preliminary to any treatment with serum therapy, utilizing a very small amount of the serum to be administered. Intravenous administration of the serum is to be advised (dilute the serum in 500 cc. of physiologic saline and allow this solution to drop very slowly).

Older Treatments: These employed sodium and magnesium sulfate in divided doses (3–4 Gm. every two hours, then every four hours). Bacteriophages have also been used with varying results but interest in them has now decreased.

The rehydration of the patient by intravenous injection of 5 per cent glucose solution with 2 mg. of thiamine added for every 50 Gm. of sugar, plus cardiac stimulants are often indicated.

The diet should be very strict at the beginning: first, liquids only, including hot drinks in small amounts. After recovery begins, cautiously add lacto-ferinose (milk and cereals, custards) and vitamins to the diet.

The diet of grated apples has been successful when applied from the onset of the disease.

In the treatment of chronic colitis, antiseptic irrigation is often utilized: Rivanol by enema or by mouth. Supportive general measures and vitamins are important.

PROPHYLAXIS

This is the same as for all the other intestinal infections of the same type, i.e., typhoid, cholera, etc.

1. Isolation of the sick and disinfection of their stools and soiled objects. Try to avoid the fecal mode of contamination.
2. Inspection of all waters for drinking and for washing of foods.
3. Measures against flies and protection of foods from flies.
4. Protection of healthy people by vaccination has been extensively employed in the form of anavaccine, even in the form of an anatoxin, and seems to have given real protection. The bodies of the microbes are too toxic to be utilized without formolization.

2. AMEBIASIS*

Definition: The term Amebiasis includes all the syndromes caused by *Entamoeba histolytica*. Amebic colitis, being the most frequent localization, is, thus, very important, especially from the viewpoint of contagion. We will, therefore, study this phase first.

HISTORY

Amebic dysentery was isolated only recently from the group of dysenteries. Lösch (1875), in Petrograd, observed for the first time the pathogenic amoeba, but it remained for Koch, and later Kartulis (1883–1887) in Egypt to establish the importance of this discovery. Schaudinn (1903) distinguished *E. histolytica* and *E. coli* and Viereck (1905) described the evolution of the cystic forms.

The inoculation of the disease into animals was shown to be possible by Hlava, Kruse, and Pasquale (1887–1894), and the transmission, experimentally, to man was shown by Walker and Sellards in the Philippines (1913). Finally, the culture of the amoebae was performed by Boeck and Drbohlav (1924).

The introduction of Emetine hydrochloride in the treatment of Amebiasis was first instituted by Sir L. Rogers (1912).

GEOGRAPHIC DISTRIBUTION

Amebiasis is a disease found predominantly in the tropics. One sees it, however, in many European countries, i.e., the Balkans, Russia, and Spain. It is also found in the southern United States and China. In 1933 an important epidemic occurred in Chicago (350 cases, 52 deaths) apparently due to an unnoticed unsanitary connection in the water system of a hotel. In the Congo the geographic distribution is very irregular and deserves further study. The infestation by amebiasis is very widespread. Between 5 and 10 per cent of the population are found to be apparently healthy carriers, even in temperate Europe and America, in spite of a high standard of hygiene. The infrequency of the passage from this state of "carrier" to the actual state of disease is not well explained.

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* Synonym, Amebic Dysentery; French: Amibiase, Dysenterie amibienne; German: Amoebenruhr.

ETIOLOGY

Entamoeba histolytica (a protozoan of the Class *Rhizopoda,* Order *Amoebida,* Family *Amoebidae*) exists in man in three forms:

1. *The invading, vegetative form;* diameter, 20–30 microns, very actively mobile through the emission of pseudopods. The cytoplasm flows on the solid substratum and is able to produce a pseudopod in any direction. This mobility is maintained only in fresh and warm stools. It is therefore necessary to examine the specimen almost immediately, or to use a warmed slide. The invading vegetative form is the cause of the ulcerations found on the intestinal mucosa. The vegetative form is also found in the muco-sanguinous portion of the feces of an acute case of amebic dysentery.

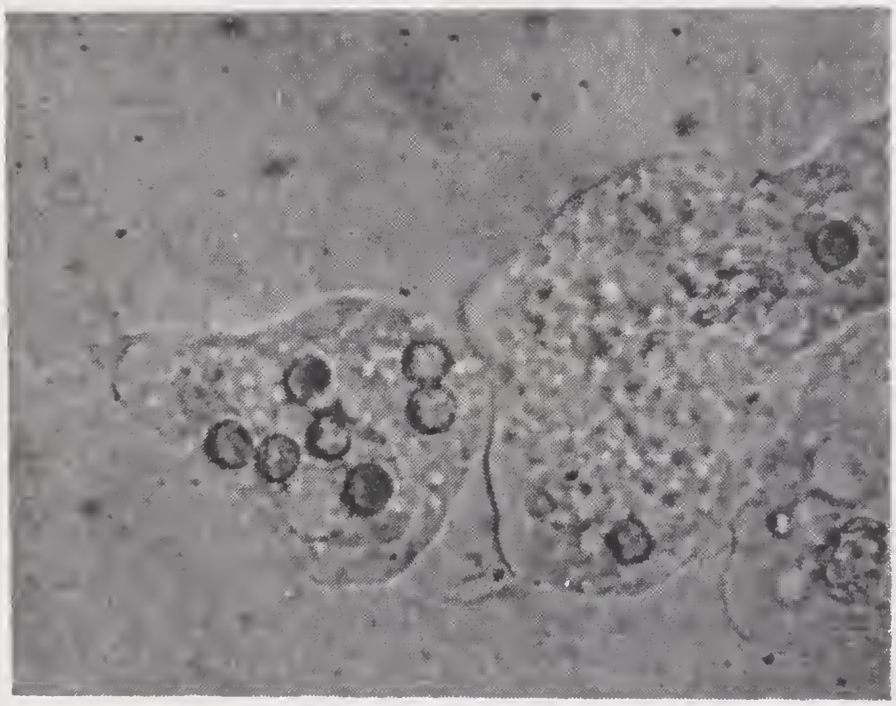

FIG. 41. ENTAMOEBA HISTOLYTICA
Wet preparation. The ingested erythrocytes are easily seen (phot. M. Chardome, Tropical Institute, Antwerp)

On direct microscopic examination, one finds that the cytoplasm is composed of a peripheral part which appears hyaline: the ectoplasm. The central part appears granular and is called endoplasm. Digestive vacuoles are found in the latter, and are produced by the absorption of food particles by pseudopods (phagocytosis). In the *E. histolytica* the food vacuoles contain red blood cells almost exclusively. Sometimes the cytoplasm is almost entirely tinted yellow by the dehemoglobinization of the red blood cells. It is rare that any other cells, bacteria, or spores of yeast are ingested. The percentage of amoebae containing the inclusions of erythrocytes varies enormously. It is scarcely ever more than 25 per cent, even less, but the discovery of an amoeba, very mobile, and containing the inclusions of red blood cells, remains characteristic of the species *E. histolytica*.

The nucleus is spherical and about 4 to 7 μ in diameter. When colored with hematoxylin-iron the characteristics are shown very clearly: a very distinct nuclear membrane dotted with fine chromatin grains, surrounding a central karyosome composed also of chromatin material.

Multiplication of the amoebae is accomplished by binary division.

2. *Precystic form:* This form is smaller, 7 to 15 μ in size and very slightly mobile if at all. It was for a long time considered as another species, *E. minuta*. Walker (1911), and Walker and Sellards (1913) were the first to indicate that this form represented a state just before encystment. The precystic form is difficult to recognize as most of its characteristics are negative rather than positive, i.e., absence of mobility, absence of food vacuoles and of red blood cell inclusions. When colored with hematoxylin-iron, the nuclear membrane contains large chromatin masses, sometimes in crescent form.

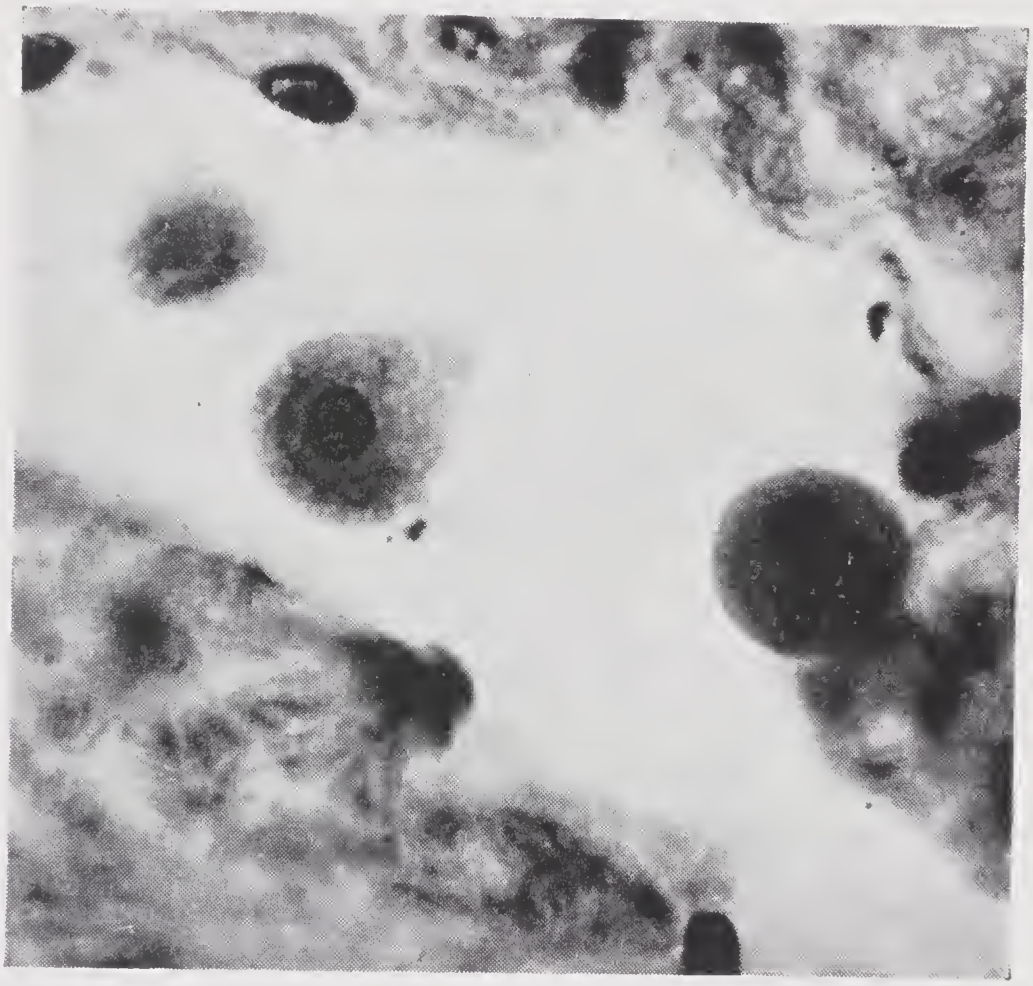

Fig. 42. Entamoeba histolytica Stained with Hematoxylin
Section of the intestinal wall (phot. M. Chardome, Tropical Institute, Antwerp)

3. *Cyst:* A wall of resistance, about 0.5 μ thick, is formed around the precystic form. The cysts are transparent, generally rounded, very rarely oblong, and measure from 5 to 20 μ in diameter. The nucleus divides into two, then into four parts, and except for an occasional anomaly, the adult cysts of *E. histolytica* contain 4 nuclei. Chromatoid bodies in the form of very refractile rods 5 to 10 μ long, and glycogen vacuoles (2 to 3 in number) are usually found in the cysts. These structures are reabsorbed.

however, through aging and after long exposure outside the host. The cysts of *E. histolytica* are killed in a few minutes by drying. They remain virulent, however, for 3 to 5 weeks in water at room temperature (Dobell). Even with favorable conditions of humidity, the cysts live only a few days at 37 C.

In the chronic cases or in the case of the healthy carrier or the convalescent carrier, the cysts are found in the mostly solid or semisolid feces. In the fresh preparation they appear as small, spherical, refractile greenish bodies in which one can distinguish 1, 2, or 4 nuclei and the chromatoid bodies. In a preparation stained with iodine (Lugol's solution) all these elements are seen particularly well.

The culture of *E. histolytica* is made easily, starting from vegetative forms or cysts, on solid egg-agar media, covered with Locke's physiologic solution and maintained at 37 C. The amoebae are nourished with sterilized starch powder. These cultures always contain bacteria which, living or dead, seem to constitute an indispensable form of food for the amoebae. Frequent transplantations are necessary.

The disease can be reproduced in certain animals (the young cat, especially, but also the dog, monkey, and rat) by the intrarectal injection of feces containing the vegetative forms (followed by closing the anus for 24 hours with collodion). Injection of the same vegetative forms into a loop of small intestine after laparotomy is equally successful (method of Deschiens). A third method of experimental inoculation is the oral ingestion of the cysts by the animal.

THE PATHOGENICITY OF *E. Histolytica*

This is a very debatable question. Indubitably, there exist subjects who, although carriers of the cysts, never develop any symptoms of the disease. These healthy carriers are relatively numerous in the temperate regions (France, for example) where clinical amebiasis of the native people is practically unknown. Brumpt thinks that in these cases the amoeba involved is not *E. histolytica* but a different species nonpathogenic for man, as well as for the cat, which he called *E. dispar*. However, Walker and Sellards had already shown that in volunteers authentic infections had been introduced with cysts taken from healthy carriers. Kessel also found that in cats, a percentage of infections almost equal in number were produced by amoebae from sick and healthy carriers. It seems that the variation in the pathogenicity of the strains of *E. histolytica* does not depend upon the virulence of the amoeba itself but on the environment which the amoeba finds in the intestine: the pH of the intestinal contents, the microbacterial flora, the existence of previous lesions, the general resistance of the patient or carrier. Vogel has shown the role played by the association of *E. histolytica* with a hemolytic Gram-positive diplococcus. The combination of hemolytic *B. coli* to a nonpathogenic type of *E. histolytica* has caused infection in cats. Numerous experiments have produced convincing work and proof of the preponderant role of the extrinsic factors in the pathogenicity of *E. histolytica*. Among these, the toxic traumatic action of croton oil on the mucosa of the colon is extremely clear (Deschiens, 1938; Nauss and Rapport, 1940). The role of the bacteriologic germs is also indisputably shown (Cleveland, 1930; Westphall, 1937; Deschiens, 1938).

There is a question as to the point at which *E. Histolytica* is pathogenic in the normal environment.: This interpretation agrees with experimental work, as well as clinical observation: the high number of carriers, all apparently healthy, would be explained; also in temperate regions, the fact that few of the subjects exposed develop the disease (not more than 10 per cent, according to Meleney); and finally, the frequency of clinical amebiasis in the tropical countries where the intestine is exposed more than elsewhere to the action of pre-existing intestinal infections (notably bacillary dysentery), exposing the mucosa to the attack of the amoebae.

Amoebae Nonpathogenic for Man:

1. *Entamoeba coli.* The vegetative form is less mobile than the *E. histolytica.* It rarely contains red blood cells but frequently ingests bacteria. Stained with hematoxylin, the nucleus has larger chromatin granules on the nuclear membrane and its karyosome is eccentric. The adult cysts possess 8 nuclei.
2. *Entamoeba gingivalis* is a saprophyte in the buccal cavity.
3. *Endolimax nana* is very frequently found in the tropics. It is a small amoeba measuring from 6 to 12 μ. Its nucleus does not have any chromatin granules on the membrane. It has a large, irregular karyosome, often eccentric. The cysts are ovoid and have a diameter from 8 to 10 μ. They contain 4 nuclei. They are distinguished from those of *E. histolytica* by the unilateral flattening of the membrane.
4. *Iodamoeba bütschlii,* common in man, monkey, and pig. It is often associated with *E. histolytica.* The cysts are uninuclear with a large karyosome. They possess a well defined iodophil body.
5. *Dientamoeba fragilis.* Only the vegetative form is known. It is very mobile and contains two nuclei. The karyosome is composed of a crown of small granules. This protozoan is probably not a true amoeba. It appears to resemble very closely the Family Dimastigamoebidae or an intermediate group between the amoebae and the flagellates.

TRANSMISSION

Man constitutes the essential reservoir of the virus. However, the monkey, pig, dog, cat, and rat harbor *E. histolytica* in natural infections. The fly and the cockroach are propagators of the disease. They ingest the cysts from the fecal material. The cysts then traverse uninjured their digestive tubes, after which the stools of the insects are infectious. The transport of the cysts is effectuated also mechanically by the feet of the insects which thus contaminate food.

The infection of man is essentially by ingestion of the cysts. The wall of the cyst is digested in the intestine, and after nuclear division, 8 young amoebae escape (Dobell). It is generally admitted that the vegetative forms ingested are destroyed by the gastric juice and do not cause infection. The possibility of such a transmission must, however, be retained because it has been performed successfully in cats and dogs (Swartzwelder, 1939). The ingestion of the cysts by man is by the following means:

1. By water which has been contaminated, and is used for drinking purposes by man or animals.
2. By foods, such as fresh fruits, raw salads, vegetables grown in gardens fertilized with human fecal material.
3. By ingestion of foods and drinks contaminated by flies or cockroaches.
4. By food and drink and table utensils contaminated by the hands of the carriers of cysts.

PATHOGENESIS AND PATHOLOGY

In the vegetative intestinal form, *E. histolytica* has an indisputable pathogenic role. This is due to its aptitude for histolyzing the tissues. The nutrition of the amoeba is effected in part by diffusion and in part by phagocytosis. The amoeba penetrates the intestinal wall, traversing the lining epithelium and glands to the submocosa, producing first microscopic lesions, and later, lesions which are visible to the naked eye. The colon is the normal site of these lesions in all its length, including the appendix. The coecum and the terminal part of the large intestine are particularly infected.

At first, there exist small nodules on the folds of the intestinal mucosa. They constitute a small colony of amoebae surrounded by a histolyzed mass of tissue. Succeeding these nodules there are small ulcers, which sometimes ultimately spread and deepen almost to the serosa. The ulcers are separated by relatively healthy zones of mucosa. The localized hyperplasias of the colon tissue have been described under the name of "amoebomas" and they can simulate a tumor on palpation or on direct vision with the sigmoidoscope.

In the chronic case, secondary infections, coalescence and cicatrization of the ulcerations, thickening and fibrosis can greatly alter the intestine (stenosis, perforation, etc.).

The histologic examination beyond the first traces of histolysis and inflammation permit one to see the amoebae in the deeper layers of the ulceration and their progression into the still healthy tissue, and also into the vessels. The infiltration remains moderate (sometimes none at all) and does not contain polymorphonuclears. The "amoeboma" is an infiltration of lymphocytes, plasmocytes, and histiocytes.

The lesions here are more localized and less inflammatory than in bacillary dysentery.

The state of the intestine in the "healthy" carriers is not well known. After various observations (Musgrave in the Philippines, Bartlett in Egypt) it can be said that it is possible to find the macroscopic lesions widespread throughout the colon, although clinically symptomless. It is possible that in many of the healthy carriers, microscopic lesions exist. In 202 autopsies performed by Faust on nondysenteric subjects (accidental deaths) there were 13 infections of *E. histolytica* of which 5 presented discrete invasion of the mucosa. If it is true that these lesions are spread in numerous carriers throughout the temperate countries of the world, they would not have been missed by the pathologists. However, the practice sigmoidoscopy has shown lesions also in subjects without clinical symptoms.

SYMPTOMATOLOGY

Amebiasis presents a range of intestinal symptoms of increasing gravity. The incubation ordinarily is indefinite, but appears to be from one to three months (experiences by Walker and Sellards, also Craig at El Paso).

The simple carriers have no clear or well defined symptoms, but are able, however, to present the discrete signs of organic disorder to an attentive interrogator and observer.

In a further stage, one notes vague disorders of the digestive tube and the nervous system. The patients appear dyspeptic and more or less neurasthenic. One sometimes asks himself at this point if the amoeba is the cause or the result (watch, therefore, the effect of treatment).

These minor forms characterize the type of amebiasis in temperate countries. Craig has described these as frequent in the U.S.A.

A little more advanced form of the disease presents the intermittent attacks of nonspecific diarrhea, with gastrointestinal symptoms more or less developed (dyspepsia, anemia, emaciation, nervous disorders, etc.).

The classic amebic dysentery usually has a progressive onset. The stools which at first are solid and of only moderate frequency become muco-sanguinous. Their frequency is often limited, but their passage is accompanied by abdominal tenderness and often tenesmus. The general condition suffers relatively little at first with absence of fever, or a very discrete one. The patient is ambulant, but shortly dyspepsia, pain, infection change the general condition and the subject loses weight, becomes anemic, and takes on a sallow color.

In certain cases, there is a state of constipation rather than diarrhea and the patient passes small quantities of muco-sanguinous stools ("rectal sputum").

This classic form, untreated or badly treated, tends to bring on a chronic state with several recurrences.

The hyperacute forms, with gangrenous debris, are more rarely found. The fever, the rapid change in the patient's general condition, may lead to death in a few days. Such cases are more frequent among children. It is always necessary to think of a possible superimposed infection, in particular, bacillary dysentery.

It is hardly necessary to describe the chronic cases with abnormal stools, general depletion of the body, neurasthenia, etc.

Intestinal complications should be mentioned: Constipation, several types of superimposed colitis, hemorrhage (rare), perforation (rather rare), stenosis (rare), etc. Gastric hypoacidity is frequent. Does this facilitate the infection?

Many kinds of clinical aspects have been observed: appendicitis, cholecystitis, which could have led to untimely interventions. Chronic dysentery, especially in the terminal intestines, may simulate cancer. It can come under the label of achylia gastrica, muco-membranous colitis, sprue, etc.

EVOLUTION AND PROGNOSIS

The amebic dysentery has a great tendency to chronicity. If not treated at all, or badly treated, it often leads the primitive to death by cachexia in three to four months. The mortality in these conditions was probably 20–40 per cent, if the form was typical. With better care, amebic dysentery could have improved, but persisted for 10 to 15 years with frequent relapses.

Modern therapy has completely modified the prognosis, and the actual mortality among the Congo natives is fixed at 3 per cent, in spite of frequent delay in the call for medical assistance. It is difficult to fix the prognosis in benign atypical cases. The mixed cases have a more serious prognosis.

DIAGNOSIS

The clinical diagnosis of amebic dysentery is delicate. The sporadic cases and the atypical and light forms are hardly recognized except by laboratory findings. In the epidemic in Chicago it was shown that in temperate countries the ailment is often unrecognized.

The true amebic dysentery is distinguished easily from bacillary dysentery. This is more epidemic, more acute, and accompanied by a well defined complex of toxi-infectious symptoms which eventually terminates in rapid death by collapse and severe dehydration. The microscopic diagnosis of a classic case of amebic dysentery is easy. In the fresh, warm stool specimen, not mixed with urine, especially in the muco-sanguinous part, one finds the large *Entamoeba histolytica*, very mobile and with inclusions of red blood cells. The diagnosis of an associated bacillary dysentery (febrile form) can be made only by the isolation of the germ on lactose media.

The microscopic diagnosis is more difficult in the chronic form. The *E. minuta* and the cysts are more difficult to identify. Fortunately the cysts preserve themselves sufficiently long in the stools to be sent to the laboratory. One can even fix the fecal material (Formol, 10 per cent) and send it to a distant laboratory.

The cases of carriers and chronic forms of the disease will demand three to six examinations on various days, and also after a saline purge, before declaring the results negative.

The deviation of the complement hardly enters into the practice. The culture can aid in the diagnosis. The cell diagnosis of the exudate of the intestinal secretion has been given with the same in bacillary dysentery (see above). A large number of polymorphonuclear cells with nuclei having a well defined shape are often seen in bacillary dysentery. Eosinophils, nucleated pyknotic bodies, and Charcot-Leyden crystals are dianostic of amebiasis.

The x-ray findings, used to determine precisely the degree of anatomic and functional troubles of the colon, are only partially successful in fixing the etiology. The sigmoidoscope is much more helpful (Manson-Bahr, Morton), not only by allowing one to view the lesion but also in permitting one to take a specimen of the exudate on the level of the lesion, which specimen can then be examined microscopically. Small intramucous hemorrhages can be observed, also multiple discrete ulcers (1–2 mm. in diameter), elevated and edematous. One can also see isolated, large ulcers by this means. In certain cases there may be isolated ulcers, indurated and surrounded by granulomatous tissue reaction, which can be mistaken for cancer. At times one can observe hypertrophied red areas, only slightly characteristic.

The chronic bacillary dysentery shows these ulcerated hyperemic areas, more extensive, very painful and indurated. Isolated ulcerations are found, resembling those in amebiasis. Small glandular cysts containing the bacilli are also observed.

Classically, it is necessary to employ the sigmoidoscope in all cases of chronic colitis for the differential diagnosis.

It is hardly necessary to say that in all cases of vague symptoms, the findings of *E. minuta* or of cysts should be interpreted with prudence. These findings justify in all cases a treatment with specific, inoffensive drugs (derivatives of Iodooxyquinoleine), the results of which will be significant. Mühlens drew attention to the subject and the aspect of resurrection which follows a successful treatment. If the deparasitation is not followed by favorable clinical results it becomes necessary to think of lesions superimposed on amebiasis. If sometimes a case of amebiasis can be mistaken for cancer, the reverse is also true.

The appearance of symptoms of appendicitis in amebiasis must be interpreted with great prudence. It may mean lesions of amebiasis and indicate specific treatment. It can also mean appendicitis from other causes. In the former case, an operation appears dangerous (e.g., the epidemic in Chicago). In a doubtful case, a control treatment should be instituted, if possible, with emetine.

A blood count has little significance except in hepatic abscesses, where there is usually a leukocytosis with polynucleosis. The noncomplicated dysentery shows only a slight decrease in red blood cells (except in cases of dehydration). The white count is almost normal.

TREATMENT

The acuteness of symptoms may at times necessitate bed rest, hot applications, opiates, and strict diet: liquid and later a lacto-farinaceous regimen.

The subacute and chronic cases are evidently more tolerant. In all cases chemotherapy should be given immediately.

Ipecac and its alkaloid, emetine.

Since Rogers (1912), use has been made of one of the alkaloids of ipecac: emetine hydrochloride. Emetine belongs to the group of isoquinoleine and its salt is a rather soluble white powder. It is best administered parenterally; subcutaneous injections (irritating: *Do not exceed concentration of 1 per cent*); intramuscular injections (slightly painful, same concentration); or intravenous injections (great caution: *one should not begin by this route*). Next to local irritating actions (keratitis by instillation in the eye) the alkaloid exercises a toxic action on the skeletal, cardiac, and nonstriated muscles, the respiratory center (increased respiration) and the vomiting center. It lowers the blood pressure by relaxing the capillaries. The elimination, in part intestinal, is slow and, therefore, a possibility exists of accumulation and intoxication. In man, one notices circulatory disturbances, paralyses due to alterations in nerves and muscles (dropping of the head, difficult swallowing), diarrhea, stomatitis, and pulmonary congestion.

It is also necessary to warn against a long course of treatment. It should not exceed the total of 1 Gm., or even better, 700 mg. Emetine may or may not take quick effect. Do not repeat the treatment within one month.

The normal dose for an adult is from 60 to 100 mg. At first, test the patient's susceptibility by injecting 30–40 mg. in the morning and repeat the dose again at night. These dosages seem necessary for a sure action against the amoeba. Children are rather sensitive to emetine. One mg. per kilo of body weight should be used for resistant children. Cardiac lesions contraindicate the use of emetine.

The action of this alkaloid is remarkable in acute and reactivated cases. After twenty-four to forty-eight hours, the stools become more normal but the deparasitation is often not complete. Hence, relapses are possible at this stage. The chronic cases often respond unfavorably. The product should not be used in the atypical cases (it is too toxic and has very little action). Certain authors outlaw it completely. To us, however, it seems still advisable to use it in all active cases and in the beginning of a treatment. It is necessary finally to resort to a supplementary therapy of iodoquinoleine.

Emetine appears to be especially effective on the tissular forms (histolytica). Its action is also manifested in vitro (cultures), even to a concentration of 1: 5,000,000. Since the introduction of this drug in the hospital at Leopoldville (1913), we can report a marked lowering of the mortality among the natives.

The iodide of bismuth and emetine (about 30 per cent alkaloid) is advised by the English authors. It should be taken by mouth: from 150 to 200 mg. per day for ten days. It is not well tolerated.* This substance is most suitable for the cases which have become chronic, and should be taken at bedtime, if necessary with opiates or barbiturates, in keratine or hard gelatin capsules.

Ipecac is difficult to administer (it causes vomiting), but the following may be tried:

Paste of Ravaut:	Syrup Carbon Bismuth subnitrate Glycerin	āā 25 Gm.
	Ipecac	4 Gm.

One teaspoonful should be taken, 2 to 10 times per day. The granulated Rhodiacarbine Specia, which corresponds to it, is easier to take and contains also iodoquinoleine.

Arsenical drugs: "914" by mouth or by injection is no longer in use, but phenyl-arsenic acids are used with success. Stovarsol (Goyl-Spirocid) is given in doses of 500–750 mg. daily by mouth, for adults. Corresponding doses are given to children. It is administered three to four days consecutively. After a rest, resume.

Carbarsone (28 per cent arsenic) is given in doses of 250 mg. twice daily, for ten days. It is repeated after a rest period if necessary. This drug is judged favorably by many observers. It is necessary to watch for sensitivity (albuminuria, exanthema, etc.). Fatal accidents have been reported even with Carbarsone. The Carbarsone oxide (arsin-oxide, trivalent) is yet little known.

Quinoleine derivatives: We owe to Mühlens and Menck (1920) the introduction, into the treatment of amebiasis, of a drug that has been known for a long time: 7.Iodo-8 oxyquinoleine-5 sulfonic acid (HSO_3) commercialized under the name Yatren (Bayer), Chardyl (Meurice), Chiniofon (U.S.A.), Quinoxyl (England), etc. It is a yellow powder, to be conserved dry and containing 36.5 per cent nonfree iodine (pure product), or 28 per cent (commercial product). This product is added to 20 per cent $NaHCO_3$ which assures its solubility. It is soluble in water at a temperature of 80 C. at 4 per cent titer (avoid contact with iron).

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* Observe the stools which become black in color when this drug is used.

Regarding the pharmacology, Yatren is considered to have a very low toxicity. It often provokes a considerable diarrhea but without colic. Some physicians in the tropics use it in small doses (500 mg.) as a laxative.

Like many other quinoleine derivatives, this is an antiseptic which also exercises a toxic effect on the amoeba in vitro. Urinary elimination gives a green staining with $FeCl_3$. Intravenous injections are contraindicated.

Posology: Orally one to three, even four, 250 mg. pills taken three times daily, while testing the sensitivity of the patient (diarrhea). Treat for seven days. Then continue the treatment three consecutive days per week for three weeks, or use the rectal mode of instillation. A total of 80 to 100 pills, taken after meals, suffice for a cure. A small amount of opium may increase the tolerance at the beginning of the treatment.

Dosage for Children: (according to Mühlens)

1 month	20 drops, solution 4 per cent, 3 times a day
6 months	40 drops, solution 4 per cent, 3 times a day
1 year	50 drops, solution 4 per cent, 3 times a day
2–3 years	250 mg. per day
Older children	500–750 mg. per day

The oral administration works favorably in most cases of dysentery. It gives better assurance of deparasitation, especially by cyst passers.

The rectal mode of administration is also advantageous and is more suitable in the chronic cases with persistent ulcerations. It should always be preceded with a cleansing enema since it has no value unless the medication is kept and absorbed. It is best administered lying down at night, after a preliminary administration of a small amount of opium. Do not exceed a concentration of 0.5 to 1 per cent. At first 1 Gm. in 200 cc. of water, then progressively increase to 1.5 Gm. per 300 cc., 2 Gm. per 300 cc., 3 Gm. per 400, 500, and 600 cc. (To be held for 20 minutes while the patient lies on the right side.) Treat in this manner for three to seven days and then space the rectal injections to three consecutive days weekly. Total dose: 20–25 Gm. Both methods can be combined in various ways, so that part of the daily dose is given directly and part by mouth; or alternate administration by mouth and by rectum.

Other derivatives of quinoleine: Iodochlorhydroxyquinoleine, or Enterovioforme Ciba, contains 41.5 per cent of iodine (pure product) and 37.4 per cent in the commercial product, to which Sapamine has been added. Prescribed doses are: 250 mg. three times daily for seven days. Then rest one week, and repeat. The tolerance for this drug is good but the experience with it is less extensive than that with Yatren.

Diiodoxyquinoleine Paramibe (Meurice) Diodoquine (68 per cent iodine) is almost insoluble and nontoxic. The dose is 1 to 2 Gm. daily. It is partially absorbed (increase of iodine in serum) and causes at times anal pruritus. The literature seems favorable to the drug.

Treatment of chronic cases: Emetine is not indicated here except in reacerbations, with hematophagic amoebae present. Manson-Bahr prescribes: (1) iodide of bismuth and emetine, 200 mg. in hard gelatine or keratine capsules at bedtime (facilitation of the tolerance by opium or barbiturates), for ten to twelve days. Toleration is difficult. (2) Associated with this treatment, rectal administration of Iodoxyquinoleine as prescribed above. These instillations, when administered with caution, may bring excellent results.

Treatment of Resistant Cases: It is necessary to consider superimposed bacterial infections. In these cases use sulfamides. (Succinyl-sulfathiazol, phtalylsulfathiazol), and penicillin, in association if desired.

Rivanol, by mouth or rectally, has antiseptic and antispasmodic properties. Its amoebicidal action is negligible.

The diet should be as generous as possible with vitamins added.

The Journal of Tropical Medicine 1947, no. 1, contains a routine treatment to which we refer as an example:

First week:	6 days with 65 mg. emetine per day. 1 million units of penicillin (33,000 units every 3 hrs.). 20 Gm. sulfadiazine or sulfamethazine.
12 days:	Emetine-bismuth-iodide, 130 mg. every evening (with luminal or opium), and Chiniofon enema.
20 days:	Diodoquine: 650 mg. three times daily.

Treatment of "Subclinical" Varieties and of Carriers: Emetine is strictly contraindicated. The less toxic drugs of the quinoleic series should be used here.

Surgical Treatment: Appendectomy followed by colonic lavage is only occasionally performed.

In an endemic area amebiasis should be considered in the differential diagnosis of all obscure abdominal conditions, especially those simulating chronic appendicitis. Appendicular symptoms can be present without actual appendicitis. In the Chicago epidemic, 32 cases of this kind were operated on and 13 of them died, which shows that these ulcerated and inflamed intestines do not tolerate surgical interference.

The appendix is very often ulcerated as a result of the frequent lesions in the caecum (40 to 50 per cent of cases) but appendicular symptoms are not a constant finding and general treatment is all that is required.

AMOEBIC FOCI OTHER THAN INTESTINAL

For practical purposes these may be divided into three groups:

1. *Unconfirmed foci:* Amoebae have been seen in the bone marrow in cases of chronic arthritis and in the lymphatic glands in cases of Hodgkin's disease. The identification of the amoebae, made on purely cytologic grounds, is very questionable. Amoebic cystitis and pyelitis have been described, sometimes associated with an intestinal fistula. Other even more doubtful cases have been attributed to a sort of amoebic septicemia. Cholecystitis and amoebic bronchitis are equally uncertain. Both bile and urine are unsuitable media for amoebae. In the bronchi, *Entamoeba gingivalis* can give rise to mistakes in diagnosis.

Many of these foci have been attributed to amebic septicemia by Greek doctors (in Egypt) but this observation has not been confirmed. Occasionally, however, amoebae are carried in the blood stream. In all these places the amoeba has not been sufficiently identified.

2. *Foci verified parasitologically, but unimportant in practice:* Amebic phagedenism of the skin at the opening of a liver abscess, fistulae in the perineal, gluteal, or abdominal regions. Amebic penile chancres even have been reported. Lastly, cerebral and various visceral abscesses are rare.

3. *Important clearly defined foci:* The chief of these are liver abscess and, more rarely, lung abscess which is usually secondary to the first.

Liver Abscess

This is caused by embolic spread of amoebae through the portal system. It is quite frequently found at postmortem examinations of dysentery patients (20 to 50 per cent in different series), but taken altogether its proportion is below 5 per cent, thanks, perhaps, to improved therapeutic measures. It has the reputation of afflicting white rather than colored subjects, and certainly men more than women and children (possibly on account of greater alcoholic excess in the former). Liver abscess is extremely rare in temperate countries in spite of the existence of many carriers. It can be found, especially in the tropics, in patients without a known history of dysentery.

Pathology: When the amoebae have arrived in the substance of the liver, usually by way of the portal system, rarely by direct spread, they begin to exercise their histolytic action. Necrotic greenish grey zones appear at first, which later break down into a chocolate colored pus. Microscopically this "pus" is chiefly composed of cellular debris, red blood corpuscles, a few white cells, and occasional amoebae. These latter are chiefly found in the wall of the abscess. The surrounding microscopic changes are not very characteristic: congestion, a little cellular infiltration and degeneration, and absence of pyogenic membrane. Long standing or secondarily infected (about 50 per cent) abscesses can show the more common yellowish pus. The abscess may be single or multiple (generally 2 or 3) and is usually situated in the right lobe. Sometimes there are numerous abscesses, giving the liver a wormeaten appearance.

Minor forms of hepatitis are perhaps relatively common. Shute (1947) reports the frequence of a positive "cephalin cholesterol" test in simple amebiasis. This test indicates an alteration of the hepatic parenchyma.

Symptomatology: Amebic hepatitis appears at many different times during the course of the intestinal infection and its progress is sometimes relatively rapid, and at other times very chronic.

Fever is almost always present but can be very variable, sometimes moderate and almost continuous, sometimes remittent with shivering and sweating. The fever is accompanied by an increasing alteration in the general condition: anemia, swarthy and slightly jaundiced complexion, insomnia, and emaciation.

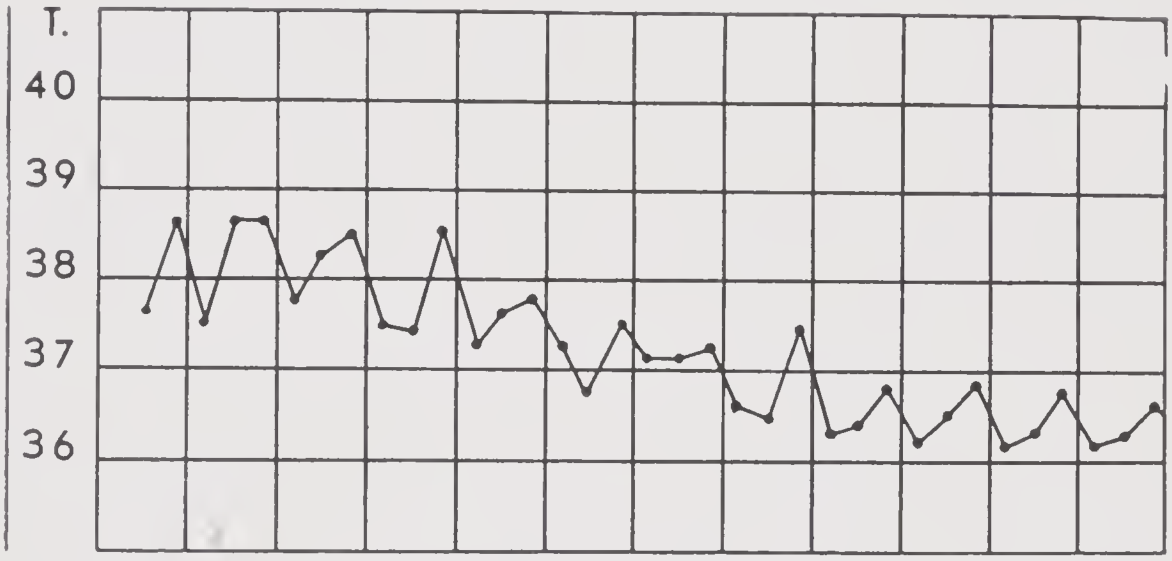

Chart 21. Amebic hepatitis influenced by emetin (patient at the Antwerp Institute)

The local signs are also very important: epigastric or right hypochondrial pain which sometimes radiates to the shoulder. The pain can, however, be vague or absent.

On examination, enlargement of the liver with tenderness on pressure is found. The right diaphragm is immobile and sometimes there are signs in the chest such as dry cough, crepitations, and pleural rub.

Evolution: Although always chronic it can proceed to spontaneous cure. The abscess sometimes opens on to the skin of the abdomen, more often bursts into the lung, or it may open into abdominal viscera, or even into the pericardium.

Prognosis is always uncertain, cachexia or an unfortunate perforation (peritoneal, pericardial) threatening the life of the patient.

Diagnosis: Liver abscess must be considered in every case of pyrexia of unknown origin with deterioration of the general condition whether the patient has or has not had dysentery. The subjective and objective signs (percussion, palpation) of liver enlargement should be sought. X-ray examination will only rarely show the abscess, as it almost never contains gas, but frequently shows the raised immobile right diaphragm. The abscess can sometimes deform the dome of the liver.

Blood examination is of great importance. Leukocytosis (12,000 to 30,000) with deviation to the left is a useful sign. Examination of the stools for amoebae (after purgation) must not be forgotten, though both amoebae and cysts may be absent.

If there are sufficient suspicions of amebic hepatitis a diagnostic course of emetine treatment is fully justified. The only certain sign is aspiration of the abscess, but this can be quite difficult and carries with it an element of risk (hemorrhage). Anesthesia may be necessary. Aspiration should be performed with not too fine a needle (8–10/10 mm.) not longer than 9 cm. so as to avoid the vena cava. Explore in several directions if necessary, aspirating constantly. The aspiration should be made over the most sensitive spot or on the mid-axillary line in the eighth or ninth intercostal space.

For abscesses situated on the underside of the liver an exploratory laparotomy may be necessary. In every case, all preparations must be made for whatever operation may be required.

The differential diagnosis of enlargement of the liver accompanied by fever is far from simple.

Kala-azar is relatively easy to eliminate; a long history, leukopenia and discovery of the parasites.

Hepatic schistosomiasis (*Sch. mansoni* or *japonicum*) is easily recognized in endemic zones by stool examination (characteristic egg).

Hepatic syphilis may be febrile and this makes the diagnosis from amebic hepatitis difficult.

Cancer of the liver, which is often febrile, is usually nodular with a large and embossed liver but nevertheless the diagnosis may be missed until found at operation.

Subphrenic abscess, suppurating hydatid cysts, cholecystitis and even perinephric abscess have caused mistaken diagnoses. Some liver abscesses have been taken for pneumonia on account of pain in the side, pleural rub and high fever.

Lastly, forms where the liver is only slightly enlarged and where general symptoms predominate can be confused with malaria, undulant fever, tuberculosis, etc. P. Manson has rightly said that the secret of the diagnosis of amebic hepatitis is to consider it. Aspiration remains the key to the diagnosis but even this can be negative when the abscess is undeveloped.

Treatment: Here emetine reigns supreme, at least in the stage of hepatitis. It is absolutely necessary to give the full daily dose of 80 to 100 mg. and a total of 700 mg. to 1 Gm. With this will be given the iodoquinoleine derivatives to eliminate the intestinal parasites. When an abscess has formed, aspiration or sometimes surgical drainage is necessary. This latter will be reserved for secondarily infected abscesses and sometimes for those of the left lobe which are difficult to aspirate. The operation is most often performed by the transpleural route after rib resection, and more rarely by laparotomy.

Lung Abscess

This is easy to diagnose if it is secondary but more difficult when primary. The diagnosis is made by the physical signs and symptoms, auscultation and above all, radiologic examination. Bronchiectasias, cancer, pleuropneumonias, and tuberculosis should be considered. The amebic nature of the abscess is brought out by the history and particularly by the presence of thick reddish purulent sputum containing amoebae. The expectoration may first occur in vomit form which is followed by a long elimination of pus. The prognosis is poor and the treatment will be based on emetine accompanied by surgical intervention if required.

Prophylaxis: The condition is usually endemic. When, however, a group of individuals is exposed at the same time to a heavy source of infection, epidemics can follow such as that which occurred in the American army in the Philippines (water-born), at the Mexican frontier in the cavalry camp at El Paso where the swarms of flies favored the spread (1916), and lastly, that at Chicago in 1933 in two hotels where the drains were accidentally connected to the drinking water supply.

From the public health point of view the problem of amebiasis must be approached from two different angles:

1. *Social Prophylaxis.* This consists in the construction of sewers, the provision of uncontaminated drinking water, the education of the people, the destruction of flies by the use of modern insecticides (DDT) and the tracking down of cases and of convalescent and healthy cyst carriers. The isolation and specific treatment of the latter is desirable but difficult to accomplish.

2. *Individual Prophylaxis.* This consists in the examination and treatment when necessary of people handling food and drink, the protection of foodstuffs and the war against flies (DDT spray) and against cockroaches (DDT or other insecticides in powder). In very endemic regions it is wise not to eat raw fruit or vegetables which cannot be peeled (strawberries, lettuce). Most experiments show that the chlorination of water does not kill amebic cysts. Chang and Fair (1941) state, however, that cysts are destroyed after 30 minutes by this means. Washing the vegetables in vinegar or permanganate has also no action on the cysts.

Tropical Liver

It is very difficult to define a single etiologic and pathologic picture for the hepatic or so-called hepatic troubles of which colonials complain: dyspepsia, tiredness, headache, vomiting, etc. Pathologic findings may be very varied: hidden amebic abscess, hepatic syphilis, primary alcholic cirrhosis or simply congestion due to overeating with lack of exercise, or again, causes outside the liver. We have already drawn attention above to the frequency of states of steatosis and precirrhosis among undernourished natives.

3. OTHER ENTEROCOLITES DUE TO PROTOZOA

The pathogenic nature of certain intestinal Protozoa has been doubted for a long while. Most authors admit, at present, that five protozoa are more or less pathogenic for man, of which two are flagellata, *Giardia intestinalis* and *Trichomonas intestinalis* (*Chilomastix mesnili* has an uncertain role) two sporozoa, *Isospora hominis* and *Isospora belli* and one ciliate, *Balantidium coli.*

These parasites are known in practically every region of the globe. However, we mention them briefly because they bring about, in the tropics, a more acute enteric syndrome.

(A) GIARDIASIS*

In 1859 Lambl discovered a protozoon Flagellate, parasite of the small intestine and biliary system of man (*Lamblia* or *Giardia intestinalis*). The pathogenic importance of this parasite has been demonstrated only since the rather recent discovery of a specific therapeutic that brings at the same time the disappearance of the parasites and of the symptoms observed.

Etiology: Giardia intestinalis (Protozoa, class Mastigophora, family Octomitidae) is a binucleated flagellate, measuring approximately 15 μ by 7.5 μ and having eight pairs of flagella. Its ventral face is hollowed at the anterior end with a cavity like a sucker used for fixation on the intestinal mucous membrane. The parasite is mostly found in the duodenum and gallbladder. In liquid environment the parasite moves very rapidly with a helicoidal movement. The forms of resistance or cysts are oval and contain two or four nuclei as well as residual flagella. When in water, the cysts remain alive for two months.

Transmission: It is achieved through direct absorption of cysts in drinking water, or on raw food. Flies carry cysts on their legs. The part of healthy carriers is considerable here (10 per cent in Java according to

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* French, Giardiose or Lambliose; German, Giardiasis or Lambliasis.

Brug, 1941, 30 per cent of the children in France according to Coutelen, 1941). *G. intestinalis* is found among monkeys, and has been transmitted to dogs. Species morphologically identical, or closely allied species are seen among rats and mice.

Symptomatology and Diagnosis: G. intestinalis provokes enteritis, generally intermittent and chronic in temperate climates. The syndrome is often acute in subtropical and tropical regions. Dyspeptic troubles linked to gastroduodenitis are not rare. Vesicular infection might be the cause of cholecystitis.

Treatment: The atabrin proposed in 1937 by Galli-Valerio was the first efficacious remedy against this particularly tenacious parasitism. In 1940 von Friedrich introduced the dichlorhydrate of chlormethoxyacridylamino-diethylaminopropanol (Acranil Bayer). Ten cg. of the product, three times a day, for five days, are sufficient to make the Giardia and the enteritic or associated hepato-vesicular syndromes definitely disappear.

(B) TRICHOMONIASIS*

The pathogenic role of the *Trichomonas hominis* (Protozoa, class Mastigophora, family Trichomonadidae), piriform flagellate, 8 μ to 15 μ long, fitted with an undulating membrane and three anterior flagella, is strongly contested nowadays. Nothing definite is known regarding the shape of the cyst. *T. hominis* resembles *Trichomonas vaginalis,* agent of a vaginitis with acid reaction in women, but the latter is larger, with a shorter membrane and four flagella. One finds *T. hominis* among numerous perfectly healthy subjects, and its presence in diarrheic stools could be explained by the existence of conditions favorable to its growth in liquid environment.

(3) COCCIDIASIS†

Isospora hominis (Protozoa, class Sporozoa, family Eimeridae) was discovered in men in 1860 (Virchow). The oocysts measured 10 μ by 16 μ.

Isospora belli (Wenyon, 1923). The infection is extremely rare (no more than 1 to 3 cases for a country have been discovered so far). It has been reported in almost every country of the world, particularly in tropical lands. Man is infected by swallowing ripe segmented oocysts. The schizogonic cycle in man is not known. In the normal or diarrheic stools of infected subjects, the oocysts are egg-shaped and elongated, measuring from 20 μ to 30 μ in length, 10 μ to 20 μ in breadth. The contents of the oocyst segments itself in two masses after having been exposed to air (sporoblasts). Each of them wraps itself in a membrane (sporocyst) and segments into 4 sporozoites. Ripe oocysts thus contain 8 sporozoites

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* French, Trichomonose; German, Trichomoniasis.

† French: Coccidiose; German: Coccidiasis.

(2 × 4). The sporozoites are freed in the intestine after the action of digestive juice over the membrane of the oocyst and that of the sporocysts.

Other germs and parasites (Dysenteric bacilli, *Entamoeba histolytica*) are often associated with cases of infection by *Isospora belli*. The same is true about infections by Giardia and Trichomonas which makes the interpretation of pathogenesis rather difficult. Nevertheless, infections limited to *Isospora belli* are spontaneously cured.

(D) BALANTIDIASIS*

This rather rare complaint is cosmopolitan and related to the infection of pigs. According to Craig and Faust (1937) in more than 25 per cent of human cases one finds direct contact with pigs. The infection in the pig is quite often mild.

Etiology: Balantidium coli (Protozoa, class of the Ciliata) is a ciliate of 50 to 100 μ in length, and of 40 to 75 μ in breadth, covered with vibratile cilia on the entire surface of the body. The endoplasm contains a reniform macronucleus and a spherical micronucleus situated in the concavity of the first. The cysts measure from 45 to 65 μ in length. The mobile form reproduces itself by transverse binary division, or by conjugation. Culture is successful in various media.

Transmission: Man is infected by swallowing cysts with food or drink infected by feces, or after direct contact with infected pigs. Human germ-carriers intervene in the transmission. The pig is the natural reservoir, but so are the monkey and man. *B. coli* have been found among wild rats (Awakian, 1937, in Moscow).

Symptomatology and Diagnosis: B. coli produces in man ulcerative lesions of the large intestine following a pathogenetic processus comparable to that of the *Entamoeba histolytica*. The symptoms are those of a typical dysentery followed in the end by cachexia. The prognosis is rather reserved and diagnosis is based on the result of microscopic examination.

Treatment: Various antidysenteric drugs have been tried with rather unequal success. Cort advises in particular enema with chenopodium oil (15 cc. in 150 cc. of olive oil). The dose in question seems enormous. It is often admitted that the rectal dose can be two or three times greater than the oral dose. Two cc. per os seem to be the admissible maximum. Strict milk diet is said to bring about cure (Silva).

4. CHOLERA

Definition: An epidemic and endemic disease caused by *Vibrio cholerae* (Koch, 1883) and characterized by a very grave enteritis with watery, bile-free stools, leading to dehydration and collapse.

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* Synonym: Balantidian Dysentery. French, Balantidiose; German, Balantidiasis

HISTORY

This disease has been known in India for centuries. In 1817 it overran the whole of Asia, in 1826, Europe and America (the epidemic ending in 1839). From 1846 to 1862 a serious pandemic raged in part of Asia. From 1864 to 1875 a fourth wave followed, again a pandemic, causing 43,000 deaths in Belgium in 1866. Lastly, from 1883 to 1896 a final epidemic reached Western Europe. In 1892 cholera was reported in Belgium for the last time (1,100 deaths) and at Hamburg (17,000 cases with 8,000 deaths).

During the last epidemic Koch isolated the germ, first at Alexandria and afterwards in India (1883–1884).

During the twentieth century epidemics have reached Russia from Asia and during the first World War they reached the Balkans.

In 1946 there were serious epidemics in China; also in Egypt (1947).

GEOGRAPHIC DISTRIBUTION

India, China, Indo-China, and the Philippines are the most important areas. In India deaths were still reaching the figure of 400,000 from 1910 to 1920, falling to 150,000 in 1935, with a recrudescence during the course of the 1939–1945 war. Australia, New Zealand, and Central Africa have escaped from this disease.

ETIOLOGY

Small, very mobile, Gram-negative vibrios which easily take the appearance of fish swimming in parallel lines when preparations are made with mucus from the intestine. It grows readily in culture on ordinary media, particularly well when these are alkaline (pH 8–9). It produces indol in peptone water and reduces nitrates to nitrites which give a red color when a few drops of concentrated sulphuric acid are added (cholera red reaction—nitroso-indol).

It acidifies several sugars without the production of gas. It does not hemolyze blood. When injected into the peritoneum of the guinea pig it produces a fatal peritonitis. The regularity with which the vibrio has been isolated in cases of the disease, and also several cases of voluntary and involuntary experimental infections prove the pathogenicity of the germ.

In the epidemiology of the disease the part played by man, especially by healthy or convalescent carriers, is very great (spread along commercial and maritime routes).

Transmission is by contaminated water, sometimes big water courses, sometimes wells and pools, causing epidemics of variable size and severity. The germ can survive in water for several weeks.

Raw food is also dangerous (salads, etc.). Flies carry the germs. Direct spread by soiled hands is possible. Religious festivals and pilgrimages play an important part in the spread of the disease in Asia. Immunity appears to be lasting.

PATHOLOGY

The cholera vibrio is strictly intestinal (ileum), but it liberates an endotoxin which acts locally (acute enteritis) and also on the whole organism. Chatterjee considers that the vibrio turns histidine into histamine which is the cause of the shock.

At autopsy, characteristics observed are: early rigor mortis, emaciation, sunken eyes, "washerwoman's hands," dryness of the tissues, the whitish watery contents of the bowel with necrosis of the epithelium, and congestion of the kidneys with tubular alterations.

Inflammatory signs are not very marked and the clinical appearance corresponds with the degree of upset of the water balance due to the excessive loss in the stools and with the degree of collapse which is partly mechanical (lowering of blood volume) and partly toxic.

The blood is concentrated (7,000,000 red cells, 12,000 to 30,000 white cells), specific gravity is high (1073 instead of 1057). There is a tendency to a decrease in alkalinity and the chloride level is very low, with resulting azotemia.

SYMPTOMATOLOGY

The incubation period is short, from a few hours to two or three days.

Forms with varying degrees of severity are seen:

1. Simple diarrhea where the diagnosis can be made only by bacteriologic examination.

2. "Cholerine" which resembles true cholera but which has a rapidly benign course.

3. Cholera gravis. The onset may be relatively mild but, either gradually, or with brutal suddenness, the typical cholera state is reached. The stools are frequent, copious, and liquid, unaccompanied by colic or tenesmus, and present the classic appearance which has been likened to water in which rice has been boiled. When left standing, the stools separate into a transparent liquid and a greyish deposit of epithelial cells. The stools are free from bile.

Frequent vomiting, associated with hiccough, tortures the patient and the vomitus may have the appearance of rice-water. The dehydration is shown by painful cramps in the muscles of the extremities, calves, abdomen, etc., and by the external appearances: inelastic skin, eyes sunken in their orbits, pinched nose, wrinkled "washerwoman's" fingers, and intense thirst. The state of collapse is reached with cyanosis, rapid and feeble pulse, very low blood pressure, superficial respiration, skin temperature low (but often a little raised in the rectum), scanty albuminous urine, or even anuria, feeble and hoarse voice.

Consciousness is frequently retained almost to the end when a semicomatose state supervenes. The cyanosed and pinched choleric mask is one of the most striking. The blood urea is increased and the bicarbonate reserve lowered.

If the collapse does not carry off the patient a stage of reaction may follow, characterized by fever, increased urinary output, and general improvement. At this period toxic or febrile manifestations, or again uremia can cause death. The fever may be very high. The mechanism of the uremia is complex: ionic disorders and also fall of blood pressure.

4. Here and there cases of "dry cholera" are seen, especially in feeble subjects. In these cases death is due to collapse before any diarrhea appears, although at autopsy the intestine is often distended.

PROGNOSIS

This is bad in forms 3 and 4: mortality 50 to 80 per cent. Treatment by saline injections has brought this figure down to 15 per cent. The introduction of sulfonamides has also improved the prognosis.

DIAGNOSIS

This is easy during epidemics and in typical cases. Isolated or atypical cases will require laboratory examinations. Violent gastroenteritis due to Salmonella may lead to confusion (isolation of the germs, agglutination, history of a suspicious contact) or also various poisons (mushrooms, arsenic). Pernicious intestinal malaria will be diagnosed by blood examination.

So far as the bacteriologic diagnosis is concerned, the isolated practitioner need only stain some exudate (Ziehl's Fuchsine diluted 1/10) and if he finds abundant curved germs moving in parallel lines like fish in a river he should suspect cholera. For culture, alkaline peptone water (pH 8) is used and also various selective media (Dieudonné, Aronson, modified by Teague and Travis, Wilson and Blair).

TREATMENT

Absolute rest, warmth, enteritis diet, sulfaguanidine or, better, sulfadiazine accompanied by transfusions of plasma. To restore the fluid loss:

1. Continuous intravenous injection of hypertonic saline:

$NaCl$	13.75	Gm.
$CaCl_2$	0.25	Gm.
Water	1000	cc.

About two liters every 6 to 8 hours for one or two days.

Or injection of normal saline, intravenously or subcutaneously, 1000 cc. every four hours, being guided by the specific gravity of the blood estimated by means of solutions of copper sulphate (normal 1,056–1,058). If the specific gravity reaches 1062 give 1000 cc.; 1063, give 1500 cc.; 1064, give 2000 cc.; 1065, give 2500 cc.

Keep the specific gravity below 1062.

2. To combat acidosis and anuria: Intravenous injections of:

NaCl	5.75	Gm.
$NaHCO_3$	18.25	Gm.
Water	1000	cc.

or, better still, a $^1/_6$ molar solution of sodium lactate.

The sodium chloride and the water are sterilized and the bicarbonate is added hot. Allow to cool and then inject. Stop the bicarbonate if there is tetany.

3. To combat collapse: Glucose 50 Gm. per liter of normal saline up to 400 Gm. per day, with the necessary insulin and always 2 mg. of thiamine per 50 Gm. of glucose. Plasma is also recommended. Toxic sedatives as far as possible should be avoided. Adrenalin is advised.

PROPHYLAXIS

This is as for other intestinal diseases, special attention being paid to the disinfection of water, the avoidance of raw food and measures against flies. The hands must be very carefully washed after attending patients or the dead.

Quarantine is based on an average incubation period of five days (stool examination of suspects).

Vaccination by means of killed germs seems to be of value. It should guarantee protection in 90 per cent of cases for ten to twelve months.

5. ANCYLOSTOMIASIS*

Definition: Pathologic manifestations due to infestation by *Ancylostoma duodenale* or *Necator americanus*. The essential symptom is anemia.

HISTORY

The discovery of *A. duodenale* by Dubini (Milan, 1838) will be remembered and its action on the blood by Griesinger (Egypt, 1854) and Wucherer (Brazil, 1866) and especially Perroncito (St. Gothard tunnel, 1880). Grassi and Parona diagnosed the disease by discovering the eggs in the feces (1878). Penetration through the skin by the larvae has been known since Looss (Cairo, 1898). *Necator americanus* was described by Stiles (1902).

GEOGRAPHIC DISTRIBUTION

These worms are found in hot and damp countries between 38 N. and 34 S. *A duodenale* is principally seen in the temperate zones, Europe, and Egypt, and in temperate Asia. It has been brought into various tropical regions. In these latter regions *N. americanus* is definitely preponderant. In all probability of African origin, it spread into the hot zones of the various continents. Very frequently an important percentage of the population is infected (50 to 80 per cent and above). In countries of temperate climates *A. duodenale* was formerly frequently to be met with in mines (coal mines in Belgium, Germany, etc.).

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* Synonym: Hookworm Disease, Uncinariasis. French, Ankylostomose; German, Ankylostomiasis, Hakenwurmkrankheit.

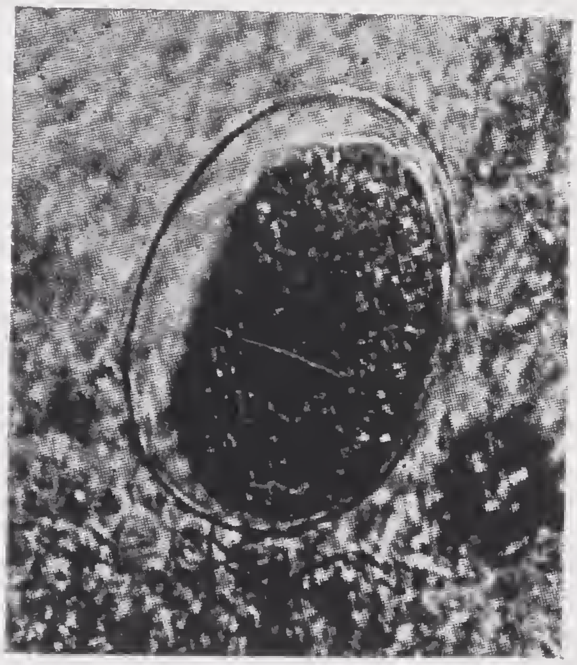
ETIOLOGY

Ancylostomiasis is due to Nematode worms belonging to the super family of Strongyloidea, family Ancylostomatidae.

They are essentially *Ancylostoma duodenale* and *Necator americanus* and accessorily *A. brasiliense.*

Ancylostoma duodenale: The male is 8 to 11 mm. long, the female 10 to 13 mm. by 0.5 to 0.6 mm. wide. The buccal cavity has two pairs of claw-like teeth. The eggs, which are probably laid at about 10,000 to 20,000 per day, measure 40 to 60 μ. The shell is oval, smooth, and transparent. In freshly passed feces the eggs possess 4 or 8 cells.

Necator americanus: The males are 7 to 9 mm. long, the females 8 to 11 mm. by 0.3 to 0.4 mm. wide. The buccal cavity does not possess hooked teeth but a pair of chitinous plates. The eggs are of a longer shape than those of *A. duodenale,* measuring 65 to 75 μ by 35 to 40 μ. Of identical habits to the *A. duodenale,* the *N. americanus* is better adapted to hot and damp climates. In tropical regions, it is generally the *N. americanus* which is prevalent though in not very great numbers (a few specimens or 2 or 3 dozen in the majority of autopsies practiced in the Congo).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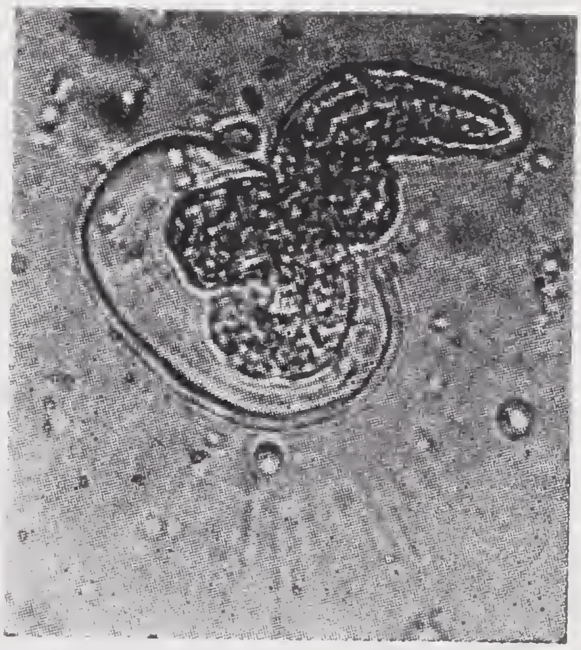
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Fig. 43a. Egg of Necator americanus
Fig. 43b. Hatching of Larva of Necator americanus
Phot. M. Chardome, Tropical Institute, Antwerp

Ancylostoma brasiliense: The length of the males is 7.5 to 8.5 mm., females 9 to 10 mm. by 0.35 mm. wide. The inside pair of buccal teeth is smaller than those of *A. duodenale.* The eggs are identical. Parasites of dogs and cats, sporadic cases of human infection have occurred in many tropical regions. Yet most frequently the larvae do not develop in man. They die after having caused a "creeping eruption."

TRANSMISSION

The eggs are hatched after expulsion of fecal matter. Under the most favorable conditions when the feces are deposited on a moist, warm, and shaded soil, the eggs are hatched within twenty-four hours. The rhabditiform larva (double esophagus) buries itself in the sub-strata and lives on bacteria and organic debris. After two molds, the larva penetrates into the damp soil. Henceforth it becomes filariform (single esophagus). Protected by a sheath against desiccation (it can live several months in damp soil), it goes to the surface of the soil, in search of oxygen.

It is at this time that it penetrates in the human skin, especially in the spaces between the toes. It then leaves its sheath, penetrates the lymphatics, reaches the blood stream, and arrives in the lungs after three days. It then moves upwards by the trachea and continues through the esophagus to the stomach and the intestine, which it reaches on the seventh day (fourth mold). The worms become full grown three to five weeks after the penetration of the larva. Transmission by way of the mouth seems of less importance than the preceding mode. It supposes penetration through the mucous membrane.

PATHOGENESIS

These worms absorb blood and eject it by the anus (Wells-Nishi). According to the latter writer, an *A. caninum* from the dog, abstracts from 0.14 to 0.84 cc. per day. It is difficult to believe that such figures could be considered as regular. What would be the fate of a man who might harbor 500 or 1,000 ancylostomes? It is to be supposed that this absorption decreases with the age of the worm. Besides the drawing of blood, the loss at the surface of the small wound must be taken into account (vasodilatation and anti-coagulation through products secreted by the worms). This despoiling action is probably the principal one. The number of worms is certainly of importance. According to Smillie the symptoms would be negligible under 100 Necators, very distinct between 100 and 500 and serious over 500. *A. duodenale* is supposed to be five times more pathogenic than Necator. Certain writers believe that one should not attach too much importance to the number of worms but rather to the hemopoietic state of the patient.

The worms live in the first part of the small intestine and provoke small ulcerations there (0.5 mm.). This might play a role (so far unproved) in allowing the resorption of microbes or toxins. A dyspepsia with resorption troubles might intervene as a result of lesions of the mucous membrane. In addition, severe ancylostomiasis is often associated with primitive deficiency diseases. This is particularly true of deficiency in proteins, lipids, and vitamins and more especially iron (Rhoads, Castle and colleagues, Cruz), whose reserves are exhausted as much by loss of blood as by insufficiency of absorption.

A direct toxic role has not been demonstrated but is possible. The nephrosis seen in dog or man may be due to blood medium disorders or to toxins. In short, the essential action would be on the blood and probably by subtraction. Recently (1941) French writers treated a case of polyglobulia with artificial infestation by 300 larvae, then after expulsion of adult worms who rendered the subject too anemic, 200 more larvae.

PATHOLOGY

The blood shows signs of microcytic and hypochromic anemia. The red cells might fall to a million or less and hemoglobin about 20 per cent or below. Eosinophilia, marked in light cases, is not appreciable in serious ones. The intestine shows small ulcerations (duodenum and jejunum) and occasionally abundant blood extravasations. The viscera sometimes show a fatty degeneration. The marrow of the long bones is red.

SYMPTOMATOLOGY

It is incontestable that in many subjects, as for instance the Congo natives, the presence of a few eggs in the stools is not accompanied by any clinical manifestation. Yet certain writers affirm that deparasitation improves the health of these carriers. More or less definite symptoms appear in other subjects. Some of these are connected with the migration of the larvae.

1. *Ground itch* (*Gourme des mineurs, etc.*): Erythemato-vesiculous, pruriginous dermatitis, observed principally on the feet, the mechanism of which is either infectious (microbes transported by the larvae) or allergic (sensitization toward the helminthic antigen). This phase of the disease often passes unperceived or is not attributed to the worms. Experimentally, the passage of the larvae through the skin produces a slight inflammation (small hemorrhage, cellular infiltration, local eosinophilia). It is said that ground itch does not appear in Egypt. The condition would mostly be brought on by *N. americanus.*

2. *Miners' catarrh:* The passage of the larvae through the lungs also provokes a state of local inflammation which is materialized by signs of bronchitis (sometimes with expectoration tinged with blood and rich in eosinophiles). In cases of massive infestation, fever, urticaria, gastro-intestinal and general disorders can be added. In spite of the presence of eosinophiles, the precise diagnosis will be difficult to determine.

3. Most important symptoms are due to the *duodeno-jejunum localization* of the adult worms. These symptoms are rarely acute and they may exist before the appearance of the eggs. Such cases have been described, namely by Van Steenis in Indonesia (1936) and by Sangster in the Pacific (1946). The following is an instructive observation of the latter on an Australian soldier infected at Bougainville:

2/11—ground itch (right leg)
2/14—coughing, expectoration
2/21—fever
2/23—diarrhea with blood
3/7—severe anemia. Hg. 5 Gm., 2,000,000 red cells, 19,000 white cells, 31 per cent eosinophiles
3/8—blood transfusion

From 3/9 to 3/11 stools with hemolyzed blood. No eggs. (5 examinations)
3/13—C_2Cl_4 3 cc. + Chenopodium 1 cc.: 2,500 Necator
3/22—C_2Cl_4 3 cc. + Chenopodium 1 cc.: 360 Necator
3/25—Transfusion
4/1—1 egg discovered in feces
4/4—Same treatment: 315 Necator
5/11—Recovery (persistent eosinophilia): absence of eggs.

Usually, however, the symptoms are chronic:

1. *Digestive troubles:* Gastralgia, sometimes involving geophagy, intestinal irregularities. In severe cases, fatal enterorrhagias or dysenteric stools are sometimes observed.

2. *Anemia:* The face is pale and puffed. The skin of the black race turns gray, the hair loses its curl, becomes woolly and discolored. After some time, the signs of severe anemia are observed: breathlessness, digestive troubles, dilatation of the heart, edema, ascitis, weakening of the muscles, sometimes albuminuria. Such subjects easily succumb to marasmus or to a complication. The temperature is usually normal or moderately high in serious cases (37 C.), or even low in cases of cachexia. Hematologically, the anemia is microcytic, hypochromic with anisocytosis and poikilocytosis. This anemia is partially due to the loss of blood, partially to gastrointestinal troubles. The iron reserves are exhausted.

3. *Psychonervous and general troubles:* Apathy and inaptitude to work combine in making this helminthiasis a disease of social importance. In young subjects infantilism both mental and sexual is observed, while adults eventually show impotency or amenorrhea. Abortion is frequent in serious cases.

PROGNOSIS

Undoubtedly many natives in tropical regions show mild manifestations of the disease, but in certain circumstances very serious cases can be observed. The white race appears to be more susceptible and in certain tropical countries ancylostomiasis plays an important part in social backwardness. Treatment is not without risks in advanced stages.

DIAGNOSIS

Without the element of endemicity, the clinical diagnosis would be very difficult here. Serious cases have the appearance of anemia and cachexias, eventually of nephritis and beri-beri. Moderate cases give the picture of cardiac involvement or sometimes psychonervous troubles. A stool examination being classic in all clinical investigations in warm climates, the diagnosis will always be reached rather soon. The simple microscopic examination of a dilution of feces is generally sufficient. Willis' procedure reveals slight infestations. More precise techniques require methods of numeration. (See Appendix C.)

Infections by males only have been encountered: in these cases the diagnosis requires the treatment followed by sifting of feces.

Special attention should be given to the following two points: (1) Too many physicians have a tendency of attributing to the Ancylostomes, after a very slight positive finding in the stools, all the patient reveals in the way of pathology. This occurs in countries in which 50 to 70 per cent of the adult population shows a similar parasitologic picture. Therapeutic trial is allowed, but must not hinder complementary clinical investigations. (2) One should avoid the confusion with other Nematodes, parasitic (see further) or even free. The latter can be absorbed with vegetables, (*Heterodera radiciola*), and have given rise to mistakes in spite of a much larger size of the eggs (80 to 120 by 25 to 40 μ).

TREATMENT

Great care must be exercised in treating weak patients: complete rest in bed, large doses of iron (4 to 6 Gm. of iron ammonium citrate or strong doses of iron salts), moderate doses of vermifuges, tonicardiacs when needed, transfusion. The vermifuges (anti-helminthics) must be given on an empty stomach and the patient kept under observation until the purgative has acted, approximately 1 ½ hours after the last dose of vermifuge. This kind of treatment must not be repeated until after an interval of eight to fifteen days.

1. *Thymol:* p-isopropyl-m-cresol $CH_3—C_6H_3—OH—CH\ (CH_3)_2$ (1-3-4). This fairly old drug still deserves to be used. It appears in the form of whitish crystals, difficult to dissolve in water (1/1000) and having the fragrance of thyme. It acts principally against Necator.

Administration: The product must be very finely pulverized while adding lactose or bicarbonate of soda. It has to be administered in capsules on account of its burning taste.

Posology: Usual dose for an adult is from 3 to 4 Gm. (taking 1 Gm. every twenty minutes or in one dose). Children receive a dose of 200 mg. per year of age (from 500 mg. to 2 Gm.). The medicine is seldom required for anyone under 2 years old. Certain physicians prescribe 3 Gm. for three consecutive days, but this treatment is very severe and it is wiser to give a strong dose once. Against pyrosis: iced water, bicarbonate.

Toxic phenomena: In spite of poor solubility, thymol is resorbed and can produce brown urine with glycuronic derivatives. Accidents are infrequent, but the product is contraindicated for those suffering from weakness, gastric or cardiac troubles. It is customary to forbid taking oil and alcohol which facilitates the solution but this view has not been proved. Bozolo who introduced the method gave thymol as a solution in wine. Joyeux prescribes as a purgative either "German spirt"* or castor oil.

Purgative: The classic method is to prescribe either sodium or magnesium sulphate two hours after the last dose of thymol.

2. *Betanaphthol:* To be dismissed because of nephritis and hemoglobinuria in patients suffering from malaria.

3. *Chenopodium oil* and *Ascaridol:* The essence of Artemisia normally contains 70 per cent of Ascaridol, an organic cyclic peroxide, the formula of which is $C_{10}H_{16}O_2$, very active against the Ascaris. The essential oil is an insoluble liquid of 0.96 to 0.99 density and with a strong flavor and smell. It has to be kept in darkness.

Administration: Adults can be given the product with water, or better in capsules. The entire dose may be given at two different times at an hour's interval with a purgative one hour afterwards or in one dose in castor oil. The latter administration is recommended for children.

Posology: Adults: two times, 0.75 cc. Children: two to three times, 1 drop per year of age or better still, a total dose of 0.1 cc. per year (this in castor oil). The prescription of Ascaridol for adults is three times, 300 mg. per dose. For children a solution in castor oil is sold as a patent medicine.

Toxic phenomena: Fairly numerous accidents have occurred, frequently on account of too strong or repeated doses. Nervous phenomena have also been observed: deafness, giddiness, fever, etc. Deaths have taken place.

4. *Hexylresorcinol:* Dihydroxy-hexylbenzol. White, waxy substance very little soluble in water, but highly soluble in alcohol or oils.

Administration: After a light meal the evening before, the drug is to be absorbed in the morning, enclosed in hard gelatin capsules, the entire dosis being taken with water. Fasting is to be continued for four hours, no alcohol should be taken; saline purgative after twenty-four hours.

Posology: Adults and older children, 1 Gm. (5 capsules); children from 8 to 10 years, 800 mg.; from 6 to 8 years, 600 mg.; and under 6 years, 400 mg.

Toxicity: Very weak, the product being especially suitable for debilitated subjects. The treatment can be taken up again after three or four days.

Action: This has been favorably judged by American observers, also in cases involving the Ascaris. It may be necessary to recommence the treatment or, after a three-day rest, to have the treatment followed by the use of tetrachlorethylene, more especially designed to fight the ancylostomes.

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* The purgative known in France as "eau de vie allemande."

5. *Halogenated hydrocarbures.*

Carbon tetrachloride: Tetraform, CCl_4, mobile and heavy liquid (D, 1.600), insoluble in water, introduced by Hall in 1921. Incontestably active (especially against Necator), it is toxic and tends to be abandoned. Like chloroform it produces sleepiness, icterus, and acute atrophy of the liver. Experimentally on animals, centro-lobular hepatic necrosis of a resolutive type and cirrhosis is observed (pigs, rats; White, 1939). In the case of severe parasitism by Ascaris, the drug can stimulate the mobility of the worms and cause obstructive disorders. Alcoholics show only slight resistance. A diet rich in calcium and in carbohydrates is favorable. In case of accident give glucose and calcium.

Dose: For an adult 2 to 3 cc. at one time (3 to 5 Gm.) followed in two hours by the saline purgative. For children, 0.2 cc. per year of age. It is wiser actually, however, to utilize the following product which appears to be far less toxic.

Tetrachlodethylene: C_2Cl_4, insoluble, heavy liquid (D, 1.6) which is used according to the dosage of the carbon tetrachloride. It is considered as definitely less toxic and as a matter of fact does not seem to have occasioned any serious accidents. It is obviously not used in the case of cardiacs and hepatics. Presence of Ascaris requires previous treatment with Hexylresorcinol, followed 3 days later by tetrachlorethylene.

Chloroform: $CHCl_3$. This is an old product which, according to Chesterman, would suit weak patients:

R.	Chloroform......................	3 cc.
	Eucalyptol......................	2 cc.
	Castor oil......................	35 cc.

Two doses of 5 to 20 cc. according to age with an hour's interval.

6. *Combined treatment:* Extemporaneously the following can be mixed: 1.8 cc. of carbon tetrachloride with 0.6 of chenopodium oil, or 2.2 cc. with 0.8, and administering a saline purgative after the taking of it, or again 1 cc. of chenopodium oil with 4 cc. of tetrachlorethylene. A mixture of carbon tetrachloride and chenopodium oil, reputed as stable, is made commercially (Bedermine Bayer).

Treatment of the anemia: Large doses of iron, liver extracts, good nourishment and rest are necessary.

Control of the treatment: This is done by sifting the feces of the first twenty-four hours after treatment, or, an easier method, by careful microscopic examination regarding the eggs. This examination does not take place until eight or ten days after treatment and by a special method or by counting. (See Appendix C.)

Creeping Eruption

This disease is characterized by the existence of an epidermic tunnel of about 1 mm. in diameter surrounded by a slight erythema increasing by 1 to 5 cm. daily and producing an eruption pruritus of irregular course. It can become papulo-vesiculous, become infected by scratching, and last for several weeks. It is especially found on the feet, hands, and seat. According to the works of Kirby Smith and colleagues (Florida), this disease is attributed to the cutaneous migration of ancylostomes larvae of dogs and cats (*A. brasiliense*), incapable of penetrating deeply in the human organism. The diagnosis must be considered with migrant larvae of Dipterous insects (Hypoderma-Gastrophilus) or Nematodes and Acariata. The larvae of flies can be recognized under a magnifying glass after cleaning the skin with cedar oil.

The treatment consists in the cauterization on the site of the insect in the case of fly larvae. For strongyloid forms, one utilizes an application of ethyl acetate on the advanced part of the lesion and covers it with an adhesive plaster for twenty-four hours, or one freezes the advanced zone to a distance of 2 cm. with ethyl chloride or carbonic snow. Oil of chenopodium can also be applied to the skin.

PROPHYLAXIS

The social prophylaxis of ancylostomiasis plays a very important part in the warm countries. The disease has become rural. In towns the sewerage system has practically vanquished it. Contamination of the soil is the essential factor. It can be avoided by establishing the following measures in the given order:

1. Construction of adequate latrines, preferably septic pits wherein the process of anaerobic fermentation kills the eggs.
2. Education of the population, principally of the children, convincing them of the danger of soil contamination (use of educational films).
3. At least a year after the two first points have been carried out, proceed to an intensive treatment of all those who carry worms. Carried out alone, this mass treatment has at least the merit of reducing serious infestations. Unfortunately these therapeutic applications on a large scale are not without risks.

Individual prophylaxis consists in avoiding the drinking of suspected unboiled or unfiltered water as well as the eating of all vegetables or fruit coming from gardens fertilized by human excrement. Finally the wearing of shoes constitutes one of the most effective means of protection for one of the commonest ways of infection.

6. OTHER NEMATODES

All nematode intestinal parasites have been observed in warm regions and especially among the native population.

The clinical manifestations of *Enterobius* and of *Trichinella spiralis* are no different there than in temperate countries and will not be described in consequence, for reasons developed in the preface.

Nevertheless, certain nematodes, *Strongyloides stercoralis, Trichocephalus trichiurus,* and especially *Ascaris lumbricoides,* although cosmopolitan, are extremely common in tropical regions and because of this are worth being described here. Others are fairly frequent, such as *Oesophagostomum apiostomum* and *Ternidens deminutus.* Finally, numbers of nematodes have been described in warm regions but in sporadic manner. We shall confine ourselves to simply mentioning them.

(A) VERY FREQUENT INTESTINAL NEMATODES

1. *Strongyloides stercoralis:* Superfamily of Rhadditoidea.

Etiology and Transmission: This intestinal worm possesses two relatively complicated cycles, the first being that of a free nematode which lives and develops indefinitely in warm wet soil, a condition found only in certain tropical climates. The male worm measures 0.7 mm. long by 50 μ wide. The caudal extremity is curved ventrally. The female measures 1 mm. long by 50 to 75 μ wide in the middle. A row of eggs fills the greater part of the body. The posterior extremity is tapering. Eggs measure about 50 by 30 μ. Rhabditoid larvae (with double oesophageal bulb) 200 to 300 μ long and 12 μ wide, hatch rapidly, feed on organic waste, and after a mould, evolve rapidly in mature sexuated forms which reproduce the cycle. When unfavorable circumstances appear, rhabditoid larvae metamorphose in filariform larvae, easily recognizable from similar larvae (Necator) by the existence of a posterior median notch. These larvae can live in the damp ground for several weeks. They are infectant for man by penetration through the skin. No animal is receptive.

The parasitic cycle begins now by a migration; circulation, right heart, lung capillaries, lung alveoli, trachea, esophagus, intestine, and most frequently the duodenum and jejunum. Worms become adult in the lungs, can copulate there, and lay eggs on the spot. The male parasite is distinguished from the free male by a larger buccal cavity. The female parasite is much more tapering than the free female. It measures approximately 2 mm. long and 30 to 75 μ wide. Its cylindric esophagus occupies the anterior third of the body. The female penetrates the intestinal mucosa, and there lays its eggs which hatch in the tissues. Fecundation of females takes place during migration and in the intestinal lumen, because only the females penetrate into the mucosa. Hologonic females, however, in the absence of males, can lay embryonated eggs by parthenogenetic mechanism.

Rhabditoid larvae out from the eggs reach the intestinal lumen. They may (a) either be expelled with the excrements and so liberate either filariform infectant larvae, or adults: the male and female free specimens.

(b) Or, in unfavorable circumstances, metamorphose within the intestinal lumen into filariform dwarf larvae which succeed in reinfecting either by penetrating on the spot in the mucosa (hyperinfection) or by penetrating through the perineum skin (autoinfection).

(c) Or, with greatly weakened subjects, and without any metamorphosis, penetrate afresh the mucosa, reach the lung, and recommence the cycle. Hyperinfection explains the lengthy duration of certain infections by *Strongyloides stercoralis* (fifteen years and more after certain patients have left the endemic region).

Symptomatology: Lesions caused by the passage of larvae to the skin (foot) and in the bronchial tubes do not differ from those observed with Ancylostoma and Necator. Surrounding the anus, auto-infection can cause urticaria and prurigo.

De Langen in Java has observed fairly important general disorders: slight fever, asthmatiform condition, expectoration, intestinal disorders, anemia, leukocytosis with marked eosinophilia (reaching 85 per cent).

Larvae have been found in sputum and in situ in the lungs. The presence of adults in the intestinal mucous membrane causes a certain degree of enteritis with chronic and even bleeding diarrhea. There is also a wasting condition.

Prognosis remains favorable, however, in the majority of cases.

Diagnosis is based on the verification of mobile larvae in fresh stools (in order not to confuse with Ancylostoma larvae which develop in feces after emission).

Treatment is not easy, probably because of the habitat of females in the intestinal mucosa. Gentian violet is prescribed, 60 to 100 mg. three times a day before food, in keratinised capsules up to a total of roughly 3 Gm. Intravenous potassium emetic is associated in ordinary doses.

Prophylaxis closely follows that of Ancylostomiasis.

2. *Trichuris trichiurus:* Superfamily of Trichinelloidea.

Etiology and Transmission: This worm was described in 1771 by Linnée under the name of *Trichocephalus trichiurus,* a term still very much in use even today. Although cosmopolitan, *T. trichiurus* is particularly common in tropical regions. Nearly 100 per cent of the population may become infected and certain subjects harbor hundreds of worms. They fix themselves in the caecum and colon by means of their anterior extremity pushed deeply into the mucosa.

The male measures from 30 to 45 mm. Its anterior extremity is long and thin, its very large posterior extremity terminating in a loop of 360° prolonged by a thorny sheath and covering a single spiculum. Very often there is only one male for hundreds of females. These measure from 30 to 50 mm. long, of which two-thirds constitute the thin anterior extremity containing the esophagus. The posterior third contains chiefly the uterus and eggs. These, brown colored, and of very characteristic barrel shaped form, are furnished at both ends with a rounded protuberance. They measure 50 μ by 22 to 23 μ. Development of the embryo is completed in ten to fifteen days when the eggs are laid on damp and shady soil.

Infestation is direct, by ingestion of mature embryonated eggs. Larvae escape from the egg only in the small intestine, and after having been nourished there some time, they reach the caecal region where they fix themselves, becoming adult after a complete development lasting nearly three months. The morphologically identical species found in the pig do not infect man, and vice versa.

Symptomatology: This is generally discrete or even nonexistent. In massive infestations, symptoms may be identical to those of ancylostomiasis and arise equally from a double processus, both mechanical and toxic.

Treatment: Oil of chenopodium, tetrachlorethylene, hexylresorcinol, expel the majority of Trichocephalus but not the totality.

The most efficient remedy would be a proteolytic enzyme contained in the latex of certain Central and South American Ficus (*F. glabrata, F. doliara*) called "leche de higueron," and used under the commercial name of Higueronia in these countries, where it is administered in a dose of 60 cc. without purging.*

Prophylaxis: This consists essentially in the education of the primitive native population, especially of the children. Danger of infection caused by lack of latrines (see further, Ascaris).

3. *Ascaris lumbricoides:* Superfamily of Ascaroidea.

Already described by the ancient Greeks and Romans, this worm has the appearance and dimensions of a lombric or earth worm. Ascariasis is the most cosmopolitan of all the helminthiases. Nevertheless, it is most prevalent in warm, damp climates where the eggs find ideal conditions for maturation of the embryo, also because of the very inferior hygienic conditions prevalent with primitive peoples.

Etiology; Transmission: Ascaris are elongated cylindric worms, with a round cephalic extremity supplied with three liplike papillae and a conic

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* In the Belgian Congo, the natives, for therapeutic and antiparasitic motives probably, frequently absorb rubber latex. There can result from this, intestinal obstruction due to massive coagulation of latex.

posterior extremity. Males measure from 15 to 30 cm. by 3–5 mm. and females from 20 to 35 cm. by 4–6 mm. A female contains several million eggs and lays about 200,000 daily. Fecundated eggs are oval, covered with a thick shell often recovered with an irregular mameloned coating of albuminoid matter that the bile usually colors a golden yellow. They measure from 45–75 μ by 35 to 50 μ and are not segmented. Nonfecundated eggs are oblong, they measure almost 90 by 40 to 45 μ. They have a slightly bumpy contour and their internal structure is constituted by a mass of refringent granules. Fecundated eggs can remain alive for several months on damp soil. Given ideal conditions for developing (temperature, 25 to 35 C.), the embryo moults inside the egg and becomes mature in ten to thirty days. The infection of man occurs by ingestion of the mature and embryonated eggs. The shell is softened by gastric juice and in the duodenum, the larva escapes, penetrates through the intestinal membrane into the lymphatics and the mesenteric veinlets, reaches the right heart and the lungs after a few days, bursts the lung capillary walls, penetrates the alveoli, remounts by the trachea and descends by the esophagus into the stomach and small intestine where it develops into an adult worm after having moulted four times during its migration. This development in man takes sixty to seventy-five days.

Although Ascaris morphologically alike are known in animals (pigs), it seems that only eggs coming from the human species reach a complete development in man. Adult worms are frequently expelled spontaneously by bowel action or vomiting.

Symptomatology: The symptoms are variable. During migration of larvae, pulmonary phenomena predominate. Hemorrhages, alveolitis are detectable microscopically, and clinically one observes in cases of intense infection, atypical bronchopneumonias, generally resolutive. The Ascaris intervenes in the Löffler syndrome, characterized by fever, eosinophilia some pulmonary phenomena with radiologic indications of resolutive condensation. Chesterman declares that personal experience in the Congo has taught him that quite a number of atypical bronchopulmonary cases in children yield to anti-Ascaris treatment, in spite of the fact that it acts rather on intestinal adults. Bronchopneumonias, following vomiting caused by living worms in the stomach, have also been mentioned. These latter, by their extraordinary numbers (up to 1,000), have succeeded in creating intestinal obstruction. By their migrations they have caused choledocian, pancreatic, appendicular, laryngal, etc., obstructions, and it seems that they have even favored the appearance of hepatic abscess. General phenomena mentioned (fever, meningism, etc.) are more vague and result probably from larvae development.

Diagnosis is based on the search for eggs. One must consider this diagnosis in any case of abdominal disorders.

Prognosis is mild as a whole (given the extension of this parasitism).

Treatment: Santonine (10 mg. per year of age up to 100–200 mg. for an adult, with calomel concurrently, or another purgative, given afterwards; Ascaridol or Oil of Chenopodium (see Ancylostomiasis); Thymol; Phenothiazine (5 to 8 Gm. per day for four days for an adult); Hexylresorcinol would be the best drug. Carbon tetrachloride and even tetrachlorethylene are contraindicated (mobilization of worms). One should not neglect treatment of this helminthiasis before any surgical intervention is undertaken.

Prophylaxis: Children are most seriously attacked, the disease being related to the excremental soiling of ground. Dig up the earth, probably contaminated, where children play. Teach in schools the imperative necessity of using latrines, the danger of hands dirtied by earth, and of vegetables and roots eaten raw.

In Asia and North Africa, the possibility has been considered that after a sudden drying up of the soil, eggs can be transported with the dust and cause infection by being inhaled.

(B) FAIRLY COMMON NEMATODES

1. *Oesophagostomum apiostomum:* Superfamily of Strongyloidea.

This nematode, very common in African monkeys (observed also in Asiatic monkeys), has been met with in man in Nigeria and East Africa (Lake Omo). Eggs are identical to those of Necator (60 μ by 28 to 40 μ). The larvae, supplied with a sheath, hatch in the ground. Men and monkeys are infected by swallowing these. The larvae cross the stomach, lose their sheath in the intestine, burrow into the mucosa of the caecum and encyst themselves, provoking small spheric cysts projecting into the lumen. Here the worms become adult, break the coating and fix themselves on the mucosa.

Symptomatology (dysentery, peritonitis) is related to the cysts bursting. Carbon tetrachloride is efficacious.

There has been discovered in Brazil (Manaos) a human case with 187 nodules on the ileum, the caecum, and the colon due to *O. stephanostomum,* a closely related species.

2. *Ternidens deminutus:* Superfamily of Strongyloidea.

This worm, fairly common in African monkeys, has been observed also in man in different parts of East Africa. In Southern Rhodesia, one meets it in 50 to 60 per cent of the natives (Sandground, 1931). It appears to exist in the Congo also, at least in Katanga, frequently associated with Necator. Its eggs differ only by being larger (on an average 85 μ to 50 μ).

It does not submit to treatment by carbon tetrachloride. After the cure of a mixed case, only the large Ternidens eggs are still to be found (van den Berghe).

(c) VERY RARE NEMATODES

Actually, it would seem that numerous parasitic Nematodes of animals, particularly monkeys, can, by accident, find an accessory host in man. This has been seen in the case of the two Nematodes previously mentioned. These Helminthiases may not be as rare as it would appear, but their diagnosis is often very difficult (similarity of the eggs).

1. *Dioctophyma renale:* Superfamily of Dioctophymoidea.

The giant kidney worm was first collected from the dog in 1782 (Goeze). It infects a great variety of animals (wolf, puma, skunk, mink, marten, otter, coati, seal, cat, ox, horse). At least 9 cases have been observed in man. The parasite appears decidedly cosmopolitan. The male worm measures from 15–20 cm. by 4–6 mm.; the female reaches 1 meter by 5–12 mm. in diameter. The ellipsoidal eggs have a thick brown shell which presents, except at both ends, strongly marked hollows. They measure 64 to 68 μ by 40 to 44 μ. The complete cycle is not known.

D. renale destroys the renal parenchyma. The latter ends by being reduced to its capsule. The discovery of characteristic eggs in the urine permits one to make the diagnosis. Prognosis is serious and the treatment surgical.

2. *Syngamus laryngeus:* Superfamily Strongyloidea.

This worm, in which copulation is permanent, is situated in the trachea of numerous birds and mammalia. It has been observed in rare cases of humans living in the Philippines, at Trinidad, Puerto Rico, Brazil. The cycle is not known.

3. *Haemonchus contortus:* Superfamily of Trichostrongyloidea.

Parasite commonly found in sheep, as well as in domestic and wild bovines. It has been observed in a Brazilian and in three Australian natives. Sheep are infected by swallowing larvae. They develop severe anemia. *H. contortus* eggs are oval, thin shelled and resemble Ancylostoma eggs but are larger (75 to 95 μ by 40–50μ).

4. *Trichostrongylus colubriformis:* Superfamily of Trichostrongyloidea.

These are very common parasites in herbivorous animals. Infection operates by penetration through the skin by infective larvae, or by swallowing them. *T. colubriformis* is a species which has been observed in man in Egypt, Armenia, India, and Australia. *T. probolurus* and *T. vitrinus* in North Africa, Armenia, Siberia; *T. instabilis*, *T. axei*, and *T. skrjabini* in Armenia; *T. orientalis* in Japan and China.

Eggs of Trichostrongylids have been seen in the Congo. They are more elongated and their poles more narrow than the eggs of Necator and Ancylostoma. Trichostrongylids do not respond to classic treatment of ancylostomiasis. They have often been the cause of repeated and intemperate treatment with useless remedies.

5. *Metastrongylus elongatus:* Superfamily of Metastrongyloidea.

Filariform Nematodes fairly common in pigs. The male measures 10 to 24 mm. by 150–200 μ, the female 20 to 60 mm. by 400–500 μ. They are found in the respiratory tract where they cause bronchitis and pneumonia. Three cases have been observed in man. The intermediate host is an earth worm. The definitive host can be infected only by swallowing infective larvae contained in an earth worm or those coming from a crushed worm.

6. *Gongylonema pulchrum:* Superfamily of Spiruroidea.

Cosmopolitan parasite of ruminants, monkeys, bears, and pigs. It has been observed a few times in man (Italy, Bulgaria, U.S.A., Russia). Infective larvae are found encysted in the cockroach which is an intermediate host. Animal and man infect themselves by swallowing an infected insect or in drinking water contaminated by dead cockroaches. Adult worms circulate in the sub-mucosa of the buccal cavity (lips, palate, tonsil region). One can extract them fairly easily.

7. *Gnathostoma spinigerum:* Superfamily of Spiruroidea.

Parasite inducing gastric tumors in cats, dogs, tigers, and leopards. It has been observed in man in Siam, India, Malaya, China, Japan, and North Queensland. Ill-adapted to man, and then only found in immature form in sub-cutaneous nodules.

8. *Physaloptera caucasica:* Superfamily of Spiruroidea.

This worm, extremely common in African monkeys, has been found in a man in South Rhodesia (Blackie). Eggs are smooth, oval, thick shelled and measure 45–65 by 30–45 μ.

9. *Thelazia callipaeda:* Superfamily of Spiruroidea.

Parasite of canine conjunctivitis (India, Burma, China), rabbits (China), and man (4 cases in China).

T. californiensis has been found also in one case of human conjunctivitus in California.

Here one must consider the possible discovery, in the feces, of free nematode worm eggs, or of parasitic plant nematodes having traversed intact, with food, man's digestive tube.

Eggs of *Heterodera marioni* (*radicicola*), nematode parasite of roots, have given rise to erroneous diagnoses. They are transparent, oval, thin shelled and measure 80 to 120 μ by 25 to 45 μ.

7. SCHISTOSOMIASIS*

Definition: It is understood as the whole of the pathologic phenomena caused by human *Schistosoma*. Thus, there exists a urinary schistosomiasis (*S. haematobium*) and enterohepatic schistosomiases (*S. mansoni* and *S. japonicum*).

HISTORY

The study of the tissues of the Egyptian mummies (Rufer, 1921) shows that the illness already existed in Egypt ten centuries B.C. In 1851 Bilharz discovered the agent or urinary bilharziasis, later called schistosomiasis. The Katayama disease (*S. japonicum*), was clinically discovered in 1883 and the precise etiology in 1904. The discovery of the cycle in aquatic molluscs goes back to 1914 (Miyari and Suzuki) and 1915 (Leiper). Treatment by antimony followed the work of Christopherson (1918).

GEOGRAPHIC DISTRIBUTION

S. haematobium: Africa: Egypt, North and South Africa, scattered foci in Central Africa (Lower Congo and Katanga) and West Africa. Asia: Arabia, Cyprus, Mesopotamia, Palestine, Iran, India (one case reported in 1945). Europe: Portugal. *S. mansoni:* Africa: Egypt, West and Central Africa. South America and Central America, Puerto Rico. *S japonicum:* The Far East, valley of the Yang-tse, Japan, Formosa, Leyte.

ETIOLOGY

The Schistosomes (family Schistosomidae) are Trematodes with separated sexes, without pharynx, with a short esophagus forking in two intestinal branches or caeca, which join each other in the hind part to form a single caecum. They have two suckers in the forepart of the body the first one buccal, the second of fixation. The male presents at the rear of the suckers a flattening of the body, the margins of which are infolded ventrally to form a groove, the gynecophoric canal. The female, more slender than the male, is enclosed, after sexual maturity is reached, in the gynecophoric groove. The Schistosomes are parasites of the blood vessels. The laying of eggs is mainly done in the small veins of the organs under the mucosa (Faust and Meleney).

1. *Schistosoma haematobium:* The male measures 8 to 15 mm. in length by a width of 1 mm. The genital mass situated at the back near the beginning of the gynecophoric canal comprises 4 or 5 testes. The female measures 20 mm. in length and 250 μ in width.

Localization: Mostly the hypogastric venous system, but also the portal and pulmonary system.

Mature eggs found in the urine measure 120 to 160 μ in length by 40 to 60 μ in width. They are oval and provided with a terminal spine.

A variety, *Schistosoma haematobium* var. *intercalatum*, was reported in the Congo by Chesterman and studied by Fisher and van den Berghe.

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* French and German: Schistosomose, Bilharziose.

The eggs are larger (up to 180 μ in length) and of lozenge-shaped form with a very long spine. The localization is always intestinal and geographically its dispersion seems to be limited to the banks of the Congo River, between Stanleyville and Kongolo. The symptoms are always mild and the cure easy.

2. *Schistosoma mansoni:* The male measures from 10 to 12 mm. in length on a width of 1.2 mm. There are 8 to 9 testes. The female, filiform, measures about 15 mm. in length and 170 μ in width. The uterus generally contains a single egg, sometimes two, and rarely the maximum of four.

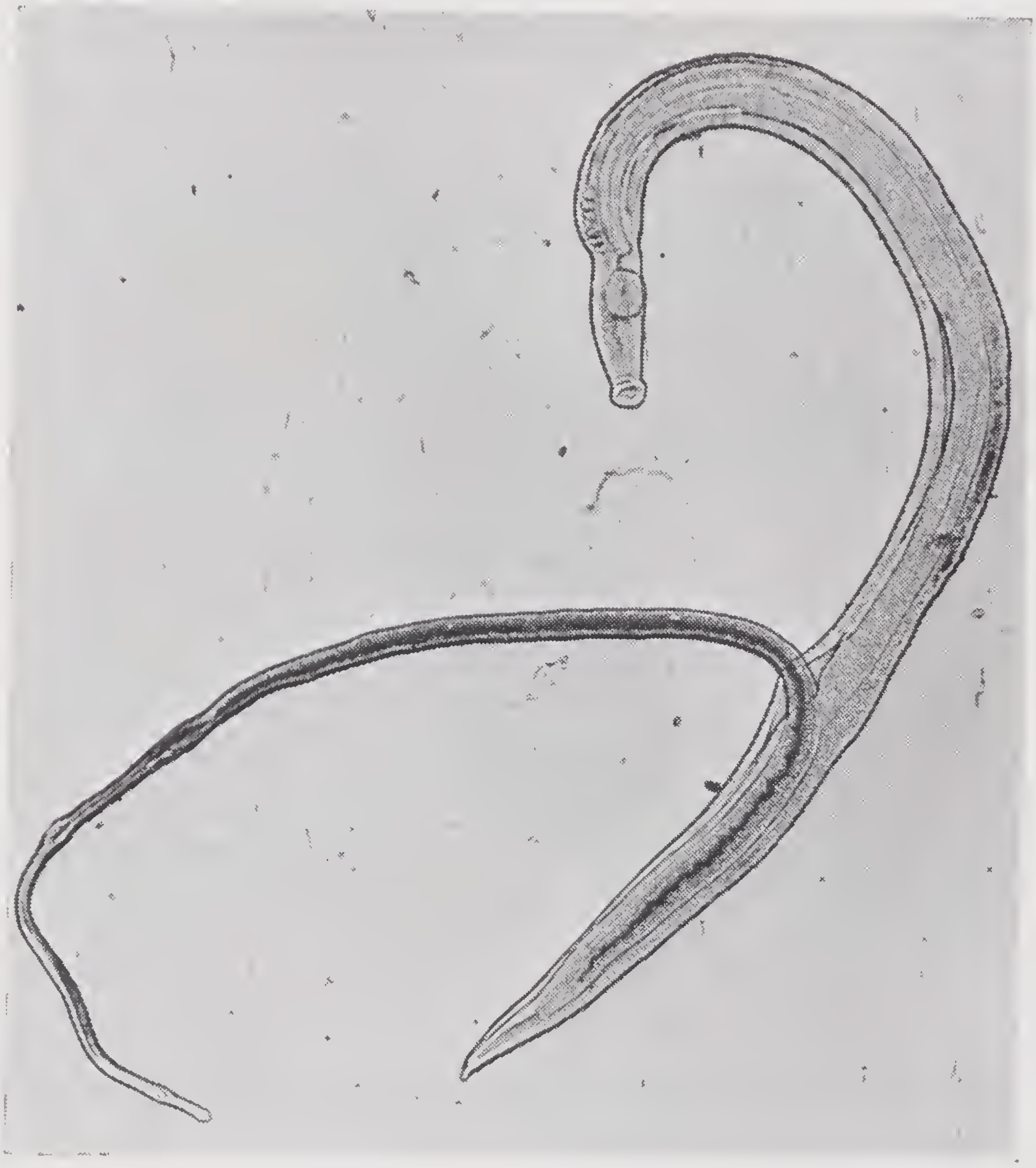

FIG. 44. SCHISTOSOMA MANSONI
Male and female partially separated (L. van den Berghe)

Localization: Portal venous system, occasionally hypogastric. The mature eggs found in the stools measure from 120 to 160 μ in length for 60 to 70 μ in width. They are provided with a well developed anterolateral spine.

3. *Schistosoma japonicum:* Unlike the preceding species, the cuticle is not covered with tubercles. The male measures from 12 to 20 mm. in length by 0.5 to 0.55 mm. in width. There are 7 testes. The female measures 25 mm. in length for 300 μ in width. The uterus contains about fifty eggs.

Localization: Portal venous system (essentially the small veins of the upper mesentery).

Mature eggs in the stools measure from 70 to 100 μ in length and from 50 to 65 μ in width. They are oval and possess an antero-lateral rudimentary spine, or rather a knob, sometimes scarcely visible and often situated in a small depression of the shell.

TRANSMISSION

In order to undergo further development the eggs must fall directly or be carried into water, where, within the following forty-eight hours, the shell ruptures. A ciliated larva, called *miracidium,* escapes and under favorable conditions penetrates into a suitable mollusc, intermediate host (Pulmonate Gasteropod without operculum for *S. haematobium* and *S. mansoni,* and Prosobranch Gasteropod with operculum for *S. japonicum*), inside which it carries on its development for about thirty days. By a phenomenon of internal polyembryonization, after two generations of sporocysts (elongated bags full of larvae), the infecting larvae, called *cercariae* are found in the mollusc's hepato-pancreas. The mobile cercariae

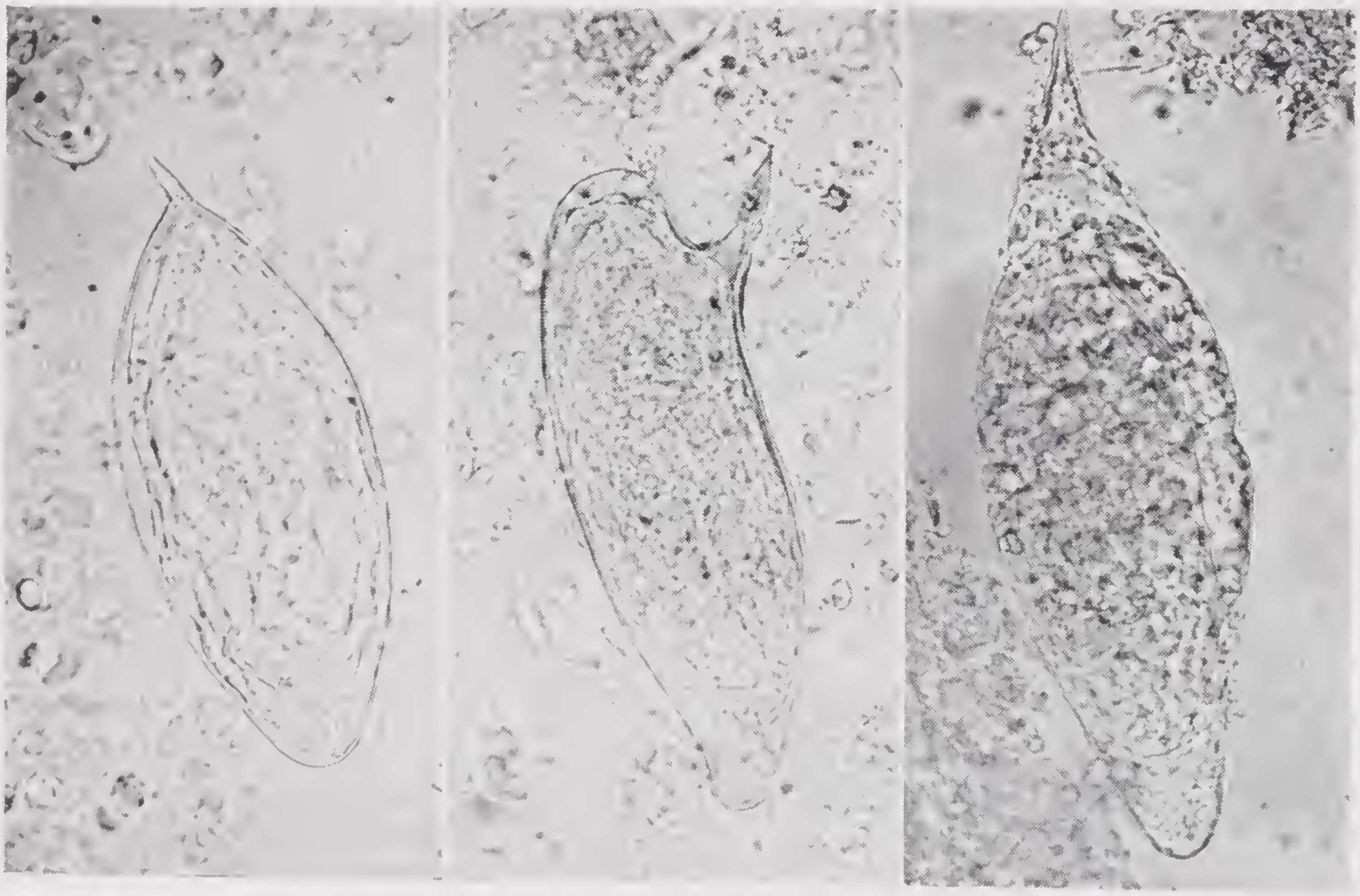
a b c

FIG. 45a. EGG OF SCHISTOSOMA HAEMATOBIUM
FIG. 45b. EGG OF SCHISTOSOMA MANSONI
FIG. 45c. EGG OF SCHISTOSOMA HAEMATOBIUM, VAR. INTERCALATUM
L. van den Berghe

of Schistosome have a leaflike body provided with two suckers and a forked and flexible tail used for locomotion. The body measures about 200 μ, the stem of the tail about 250 μ in length by 30 to 40 μ in width and each of the branches of the fork, about 50 to 75 μ in length. Extremely mobile, the cercariae escape for many months from the infected mollusc. In the water where they swim freely, mainly at the surface, they live only 24 to 36 hours. Their evolution continues only when they have penetrated through the skin or the mucous membrane of a favorable definite host. The latter gets infected while bathing or with drinking-water. Only the anterior part or body of the cercaria (the tail gets detached from the body) penetrates (in less than an hour) through the skin. The young Schistosomes or Schistosomules are found at first in the lungs where they have been carried by the veins, the heart, and the pulmonary arteries. They are found in large numbers in the capillaries of the lungs which expand appreciably. They penetrate into the veinlets, reach the left heart, and through the arterial system arrive in the arterial capillaries and the veins. It seems, however, that a certain number of Schistosomules do not follow

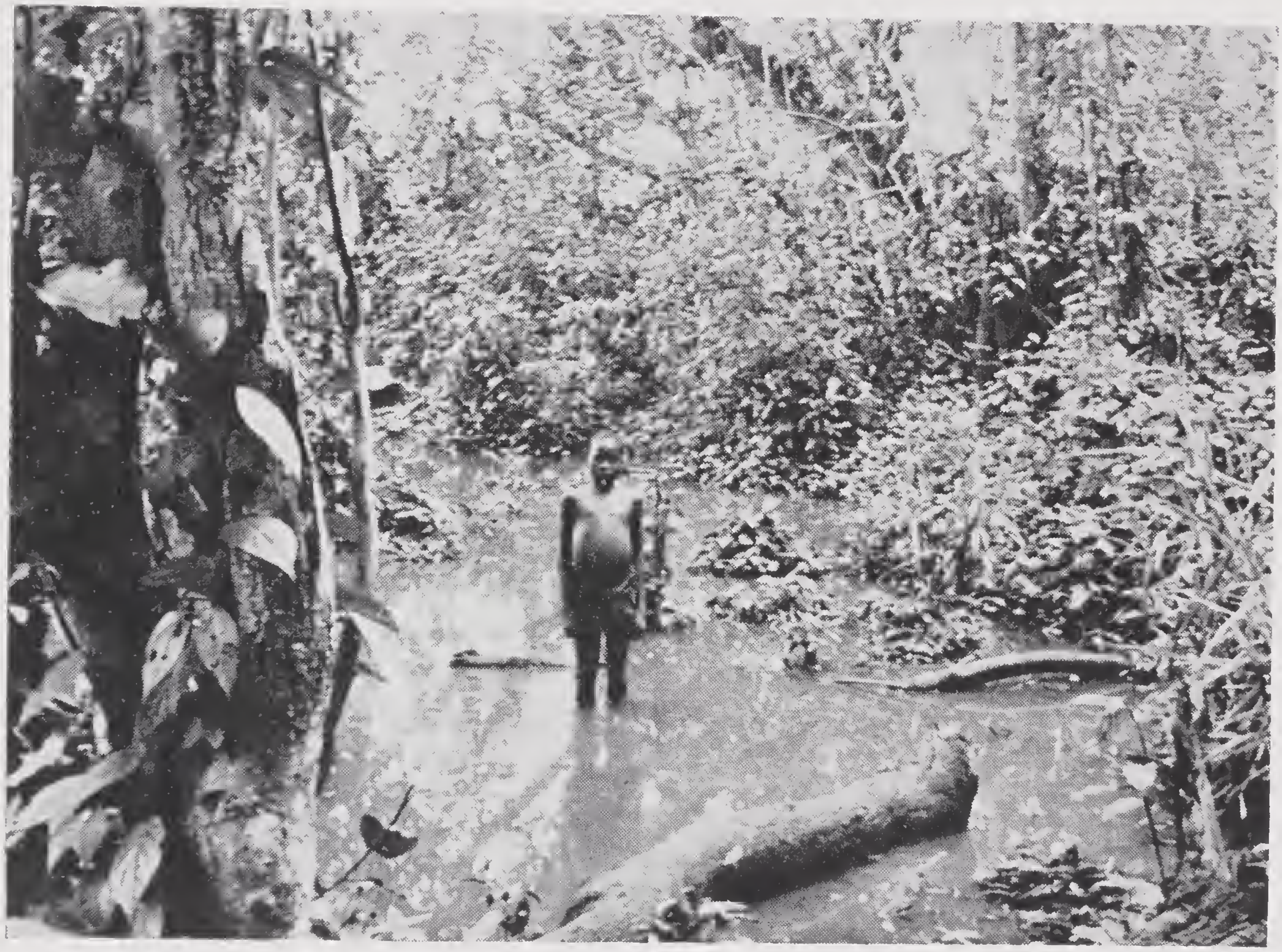

Fig. 46. Bilharzial ascitis

Boy with bilharzial ascitis (*Schistosoma mansoni*) standing in a pool where many *Planorbis adowensis* were found infected (L. van den Berghe) the blood channel, but leave the lungs directly and through the mediastinum, the pleural cavity, and the diaphragm, penetrate into the liver and the portal system. Nevertheless, the growth of the young Schistosomes occurs mainly in the hepatic venous system. When this development is concluded, the Schistosomes leave the liver and, making their way against the blood stream of the portal circulation, arrive in the tiny venous ends of the mesenteric and urinary systems. Copulation takes place at these sites, but also in the liver where the Schistosomes can remain or perhaps return (van den Berghe), and in various organs where they may appear in the course of their migration, the determinism of which has not been established. The laying of eggs begins within about forty or fifty days after the infestation by the cercariae. The Schistosomes live and lay eggs for an average of eight to fifteen years. The eggs, which are laid in the proximity of the intestinal and vesical lumen, penetrate the mucous membranes and reach the outside where they insure the reproduction of the cycle. A large number of eggs are lost through embolization in the liver and other organs.

The reservoir of virus for *S. haematobium* and *S. mansoni* is essentially human. Natural infections have been observed among various monkeys, and experimentally, monkeys, rats, mice, and hedgehogs are susceptible.

The reservoir for *S. japonicum* is mainly human but a large number of animals also are susceptible: dogs, cats, rats, mice, field vole, cattle, buffaloes and horses are naturally infected. Congenital infections have been reported among children.

The main mollusc vectors are:

- *S. haematobium:*
  - Bulinus truncatus (Tunisia, Egypt)
  - Bulinus tropica (South Africa)
  - Physopsis globosa (West Africa, Rhodesia)
  - Physopsis africana (South Africa, Belgian Congo)
  - Planorbis dufourii (Portugal and Morocco)
- *S. haematobium var. intercalatum:*
  - Physopsis africana (Congo)
- *S. mansoni:*
  - Planorbis boissyi (Egypt, Abyssinia)
  - Planorbis alexandrinus and herbeni (Sudan)
  - Planorbis adowensis (Belgian Congo)
  - Planorbis pfeifferi (Rhodesia)
  - Planorbis sudanicus (Nyassaland)
  - Australorbis glabratus (syn. Pl. guadaloupensis) (Venezuela, Antilles)
  - A. olivaceus and centrimetralis (probably synonymous for A. glabratus (Bazil)
  - Tropicorbis havanensis (experimentally in the United States)
- *S. japonicum:*
  - Katayama nosophora (Japan, Coast of China)
  - Oncomelania hupensis (Valley of the Yangtse)
  - O hydrobiopsis (syn. Blanfordia quadrasi, syn. Schistosomophora quadrasi) (Leyte).

PATHOLOGY

The pathogenic factor in these helminthiases is mainly the egg which plays the part of a more or less irritant foreign body in the visceral walls and creates inflammation of granulomatous character with tubercles. Höppli's work has shown the presence of toxic matter secreted by the eggs (*S. japonicum*). Various anatomic processes are added over these first lesions, eventually following microbic infections.

A number of eggs also reach various organs, either through embolization or through direct laying: liver (mainly *S. mansoni, S. japonicum*), lungs (*S. haematobium*). Hepatic lesions, due to *S. mansoni*, or *japonicum*, are principally caused by eggs irregularly embolized in the parenchyma. Bilharzian "pseudo-tubercles" are formed and ultimately constitute foci of sclerosis. The most frequent lesions are situated in the portal spaces where the fibrosis becomes very dense, forming large lumps of connective tissue (periportal cirrhosis, "pipe stem" cirrhosis). In the lungs one observes sclerosis as a result of granulomes. Eggs have been found even in the nervous system and this contingency is rather frequent with *S. japonicum*, causing serious lesions in the nervous system. The egg of this worm seems to be particularly toxic, causing acute inflammatory infiltrations. This egg is very abundantly laid.

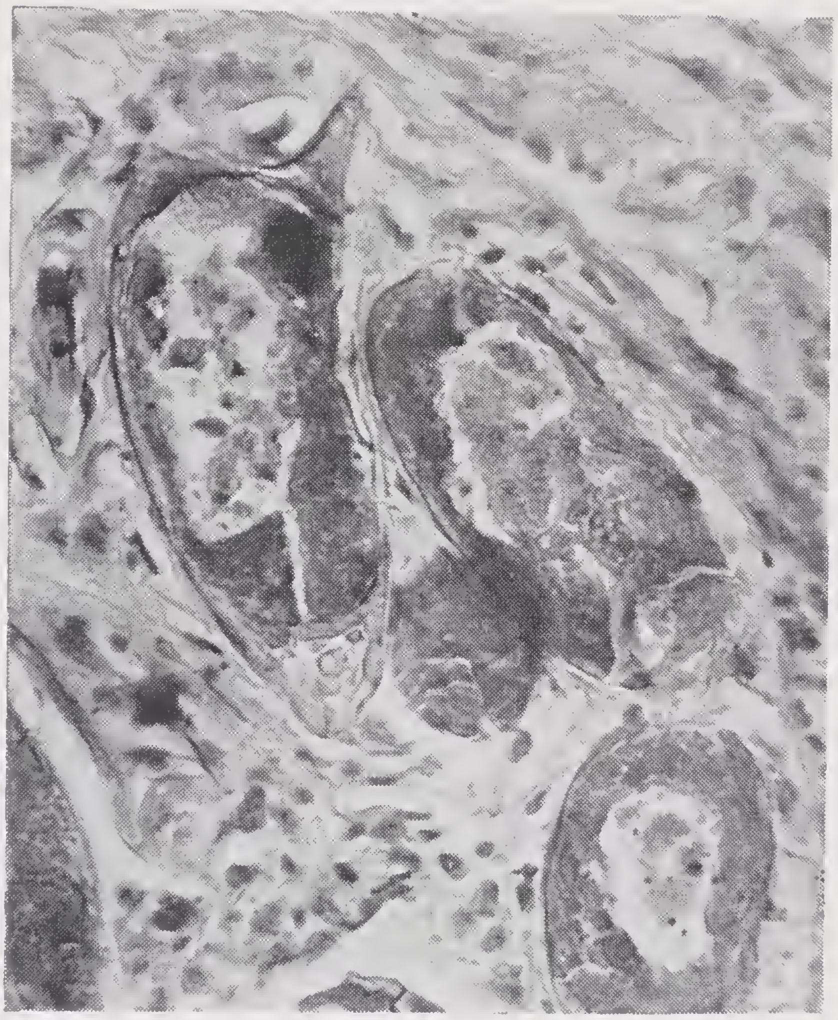

FIG. 47a
Eggs of *Schistosoma mansoni* in a section of a rectum papilloma

Adult worms (*S. mansoni*) can cause endophlebitis, particularly in the liver. They reject a blood pigment, which is fixed by the Kupfer cells, giving a typical aspect to liver tissue. The phenomena at the onset of the illness seem to be in relation with toxic substances or at least with allergenes (proteins of the worms).

S. japonicum, laying more than 300 eggs daily, is more pathogenic than *S. haematobium* (30 eggs) and *S. mansoni* (3 to 4 eggs).

All chronic inflammations caused by the eggs can take a papillomatous aspect or, in addition, degenerate in cancers. Cancer of the bladder is ten times more frequent in Egypt among the bilharzians than among subjects free from parasites.

(A) URINARY SCHISTOSOMIASIS

Symptomatology

Dermitis has been reported due to the penetration of cercariae; this is more specifically true about nonhuman cercariae.*

There is an incubation of about one to two months and the infestation can remain asymptomatic with elimination of a few eggs, or, on the contrary, when the parasites are more numerous, it can become clinically noticeable.

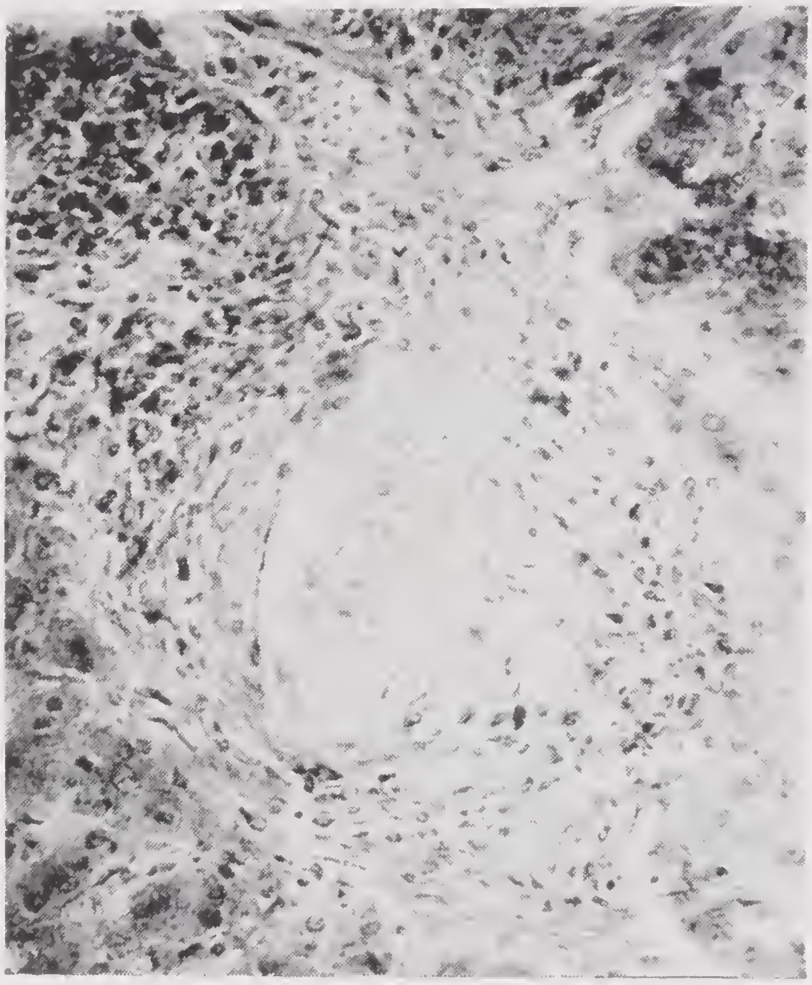

Fig. 47b

Pseudotubercle with one egg of *Schistosoma mansoni* in the section of the liver cirrhosis (L. van den Berghe)

In a first toxi-infectious stage one can observe: fever, cough, malaise, urticaria, edema, eosinophilia. These phenomena are attributed to the migration into the human body of the schistosomules and to allergic reactions.

The really typical symptoms, which appear about the third month, are due to the accumulation of eggs in the vesical wall. The result is a state of inflammation with the aspect of papulae-like grains of sand, sometimes

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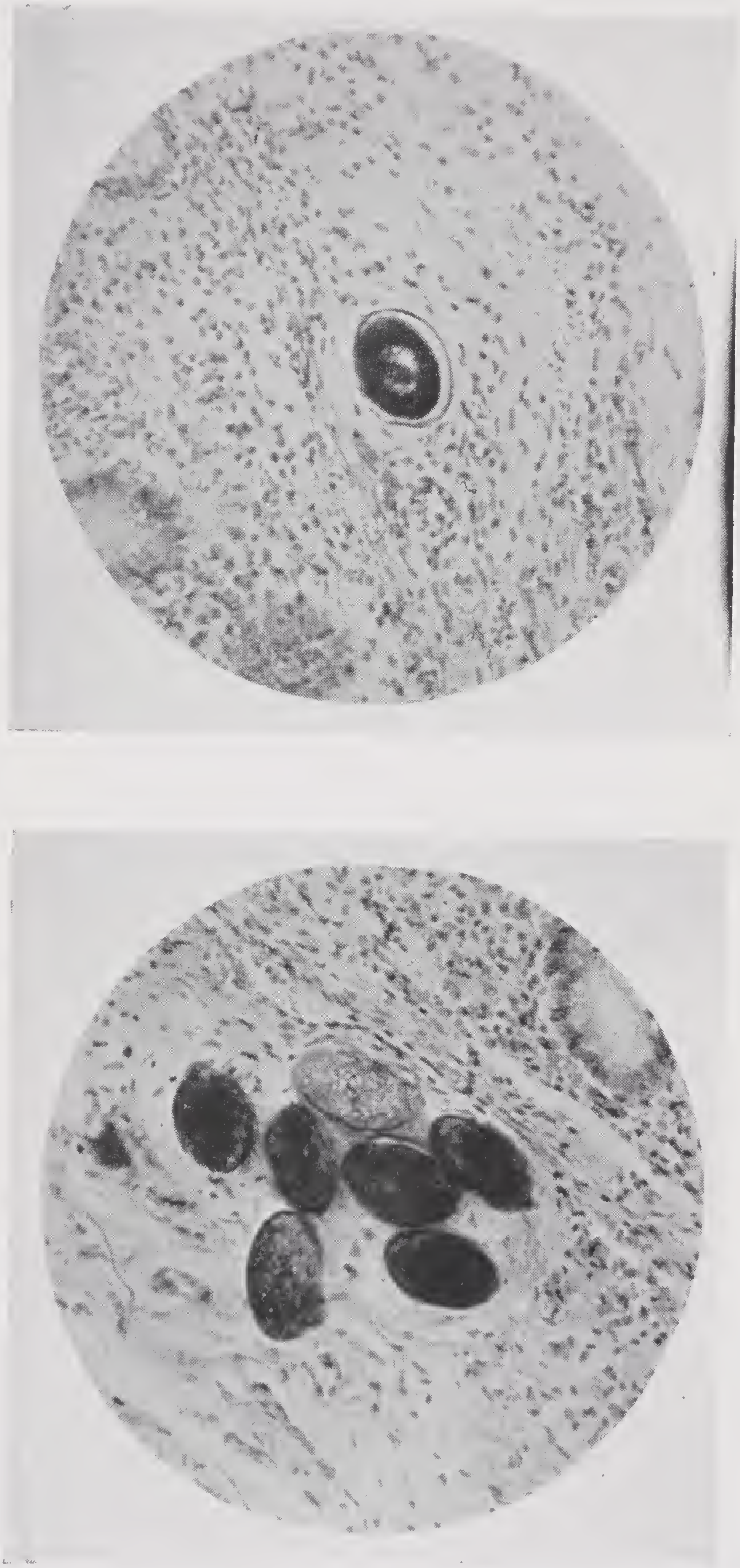
* The swimmers itch has been especially observed in the U.S.A. Burning feeling of the skin when leaving the water, small red maculae soon after, then pruritis later on, papulation and sometimes pustulation. There may be urticaria. Cured in a few days. Also observed in France (Desportes, 1944–1945).



FIGS. 48a AND b
Eggs of *Schistosoma japonicum* seen in the intestinal wall (coll. Tropical Institute, Antwerp)

of ulcerations, sclerosis, papillomatosis. Superadded infections, calculis, and even cancerization can complicate the situation.

The typical symptom is a terminal hematuria (Egyptian hematuria) with eventually some pain of the vesical type.

The clinical aspect in the region of the kidney, of the bladder, and the genitals may include: purulent cystitis, pyelonephritis, nephritic colics, hemospermia, vesical papillomes, penio-scrotal fistulae, elephantiasis of the penis, vaginitis, metritis. In the course of time, one observes neoplastic transformations. Post-hemorrhagic anemia is observed. In Cairo, the worm is the more or less distant cause of many interventions on the urinary organs.

Among the aberrant localizations intestinal localization must be mentioned (see further). Moreover, among 70 per cent of infected subjects, eggs in the pulmonary tissue with granulomatosis and sclerosis are observed.

The embolization of the vena cava may easily begin at the hypogastric plexus. Chronic pneumopathy simulating tuberculosis and most probably alterations of the right heart may result. In the Rand, Turner has noted that such pulmonary localizations are more frequent among subjects dying of diseases of the respiratory system than among those dying from other causes. Black (1945) has described cutaneous papulae containing eggs among Europeans infected by *S. hematobium* (2 cases).

Prognosis

It varies considerably, from cases without clinical importance to the most serious disorders. The latter, however, are often the result of infectious or other complications.

Diagnosis

It would be clinically difficult but for the knowledge of endemicity. The microscopic examination of the urine is typical (large eggs with terminal spine). It is obvious that besides the parasitologic diagnosis, a urologic diagnosis is necessary in order to precise the state of lesion.

The methods of deviation of the complement (Fairley) have been, until now, very little used.

Treatment

1. Emetic of potassium or, better, of sodium, used as for sleeping sickness up to a dosage of 1.20 Gm.–1.50 Gm.–2 Gm. gives many cures in cases without complications. It is more advantageous and often necessary

to make two average cures (1.20 Gm.). Once the active single dose is reached (100 mg.), one often gives the medicine every other day.

It may also be used in injections: 200 to 500 mg. pro die, 5 to 7 Gm. in all. The results of this method are less definitely established.

The disadvantages of emetic (necessity of venous injection, intolerance, collapsus) justify the recourse to other antimonials.

2. *Fouadine,* trivalent antimonial derivative of Pyrocatechin, which can be injected in the muscles, is less toxic but also less active (this element is, however, less toxic intravenously).

The following is the recommended posology:

Adults: 15 injections, the first of 3.5 cc., and the following of 5 cc. in about one month. Children: Injections varying from 0.5 cc. to 1.5 cc., according to age.

3. *Trystibine:* venous: adults 250 to 500 mg. once or twice a week, in all 7 to 8 Gm. in two months.

4. *Stibilase:* venous: adults: Injections, trial 100, then 150 mg., then ten times 250 mg. every other day. Total dose: 2.75 Gm.

5. *Anthiomaline:* intramuscular: adults: Injection every other day of 1 to 4 cc., then 4 cc. twice a week. Children (12 years old): 0.5 cc. then 1.5 cc.

Accelerated antimonial treatment: Recently certain authors (Alves, 1945) have shortened and intensified the treatment with emetic of sodium (solution of 1.5 per cent in glucose water). Injection for two consecutive days at 9 A.M., 12 noon, 3 P.M. for a total dosage of 12 mg./Kg. of body weight. The experiment is still too recent to allow an estimate of its value.

6. *Emetin:* Constituting a source of variable efficacy, it has the advantage of being injectable in the muscle (see posology of amebiasis).

Local complications are in the domain of surgery.

Control of the treatment: All active treatment is followed more or less rapidly by elimination of abnormal eggs without living embryos. Unfortunately these results are not always lasting, and normal oviposition begins anew. At least one month of observation after the treatment seems necessary before one can consider a cure.

Emetic, in spite of its inconveniences, still remains the surest weapon (16 per cent of relapses for emetic against 70 per cent for fouadin in equiantimonial doses in case of *S. japonicum*).

(B) ENTEROHEPATIC SCHISTOSOMIASIS

It is due to *S. mansoni* and, in the vicinity of Stanleyville (Congo), to *S. haematobium* var. *intercalatum. S. haematobium* is also occasionally noted in the intestine.

Symptomatology

Just as for *S. haematobium*, a great number of asymptomatic or oligosymptomatic cases are encountered. The already described cutaneous and toxi-infectious symptoms have also been observed here. The symptomatic state appears about the second or third month following infestation.

In mild cases the symptoms are vague gastrointestinal disorders with occasional diarrheic episodes and frequently passage of sanguinous mucus covering the stools, which are otherwise more or less normal. There may be pain and tenesmus. Notwithstanding that a patient having eggs in the colon may have some in the liver, this discrete hepatic infestation has no clinical expression.

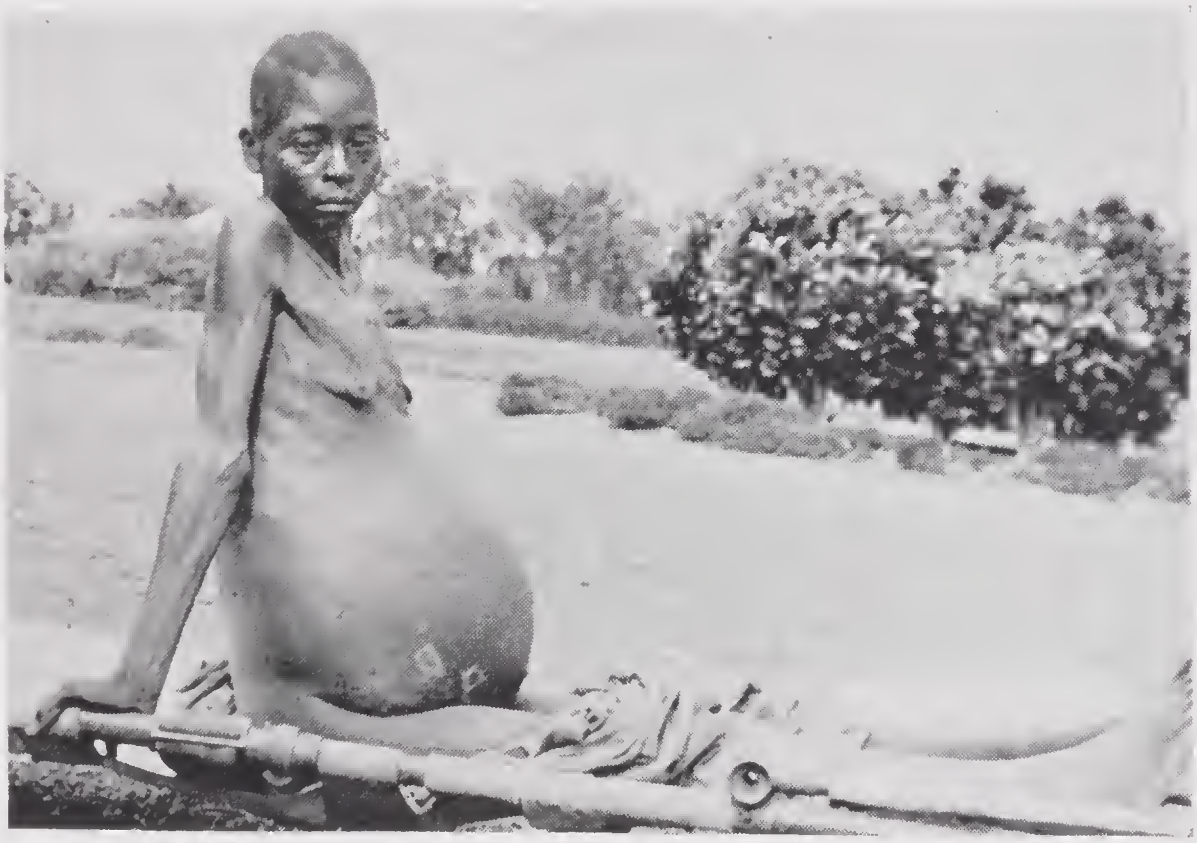


FIG. 49
Advanced case of cirrhosis with *Schistosoma mansoni* in the Uele (L. van den Berghe)

In case of mass infestation or repeated infestation, the symptoms become more acute, with a diagnosis of bilharzian dysentery: pains, repeated mucosanguinous stools, with little or no effect on the general state of the health in most cases.

Van den Berghe has reported during the past few years violent hemorrhagic enteritis resulting in death within fifteen days. This might be the result of a single massive infestation. The mechanism of these hemorrhages is still little known; it does not seem to be postcirrhotic hemorrhage, judging from the aspect of the subjects (absence of ascitis) but one must be able to eliminate additional infections.

In chronic cases, the rectum shows papillomatosis, prolapsus, fistula, sometimes pseudo-tumoral productions on the margin of the anus. The appendicular localization may be taken for ordinary appendicitis. Subserous bilharzian tubercles, with abdominal pains and palpable masses in the abdomen, may make one consider abdominal tuberculosis or sometimes appendicular peritonitis.

It is also at this time that signs of hepatic cirrhosis appear: gradual alteration of the general state of health, fever, anemia, ascitis, hepato- and splenomegaly. In the end the subject dies of cachexia and hyposystole after having eventually presented atrophic cirrhosis. Sudden death through hematemesis (rupture of esophageal varix) is reported in the Congo.

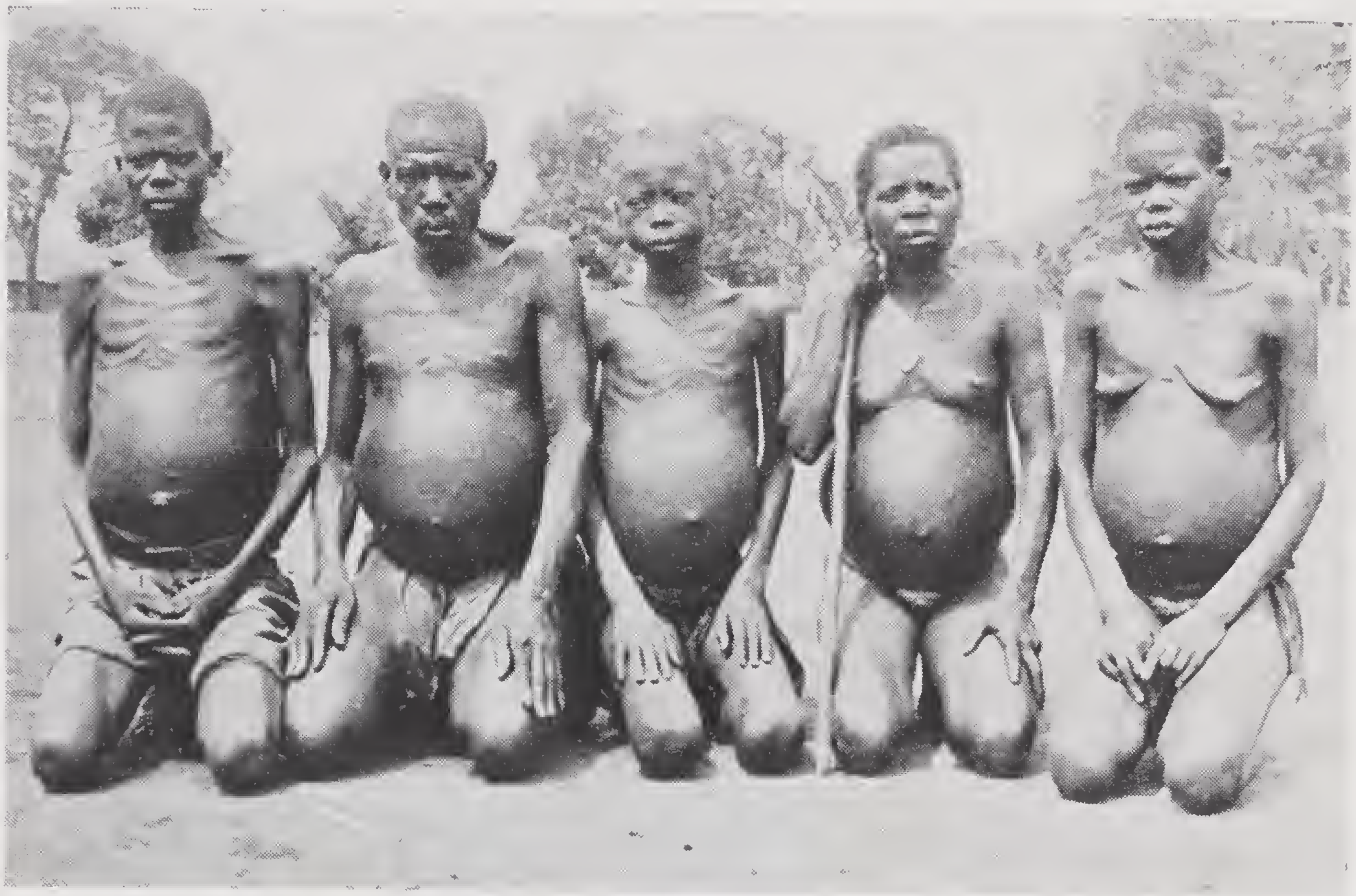


Fig. 50

Cases of cirrhosis in the Uele, one of them a boy of 10 (L. van den Berghe)

Aberrant localization can be observed in the urinary organs (rather rare). Myelitis with the presence of eggs has also been described.

Egyptian Splenomegaly, accompanied by progressive alteration of the general state of health, nearly always seems to be related to processus of hepatic cirrhosis. According to some authors it may be a hypertropic splenitis due to the accumulation of eggs in the spleen.

The female of the species seems to stray rather easily and worms and eggs have been found in a large number of organs including the medular tissue (eggs), pancreas, abdominal ganglions, lungs.

Lesions of the lungs (the clinical and radiologic aspect of chronic pneumopathy can simulate tuberculosis) particularly can assume a very great importance. The localization of the worms in the pulmonary arterioli, or sclerosis consecutive to accumulation of eggs, can create a syndrome of hypertension in the pulmonary artery with dilatation of the right heart (syndrome of Ayerza).

Prognosis

Prognosis is variable. It is severe in the forms with ascitis, very serious also in the highly hemorrhagic forms mentioned above. Hepatic or intestinal cancerization is possible.

Diagnosis

This is clinically difficult except for the knowledge of endemicity. Microscopic examination of the stools facilitates it (large egg with side-spine, except *S. haematobium var. intercalatum* which has a terminal spine). The method which uses brine must not be used for the Trematode eggs. Rectoscopy can reveal papillomatosis.

Treatment (see above) consists of various antimonials (trivalents). Slightly advanced cirrhosis no long responds to antimony.

(C) JAPANESE SCHISTOSOMIASIS

Symptomatology

The various stages mentioned in the other varieties are also observed here. The dermic phenomenon of the penetration of cercariae is irregular and mild. A dry cough is observed within a few days. Two or four weeks after the infection, phenomena of a toxi-infectious aspect appear: fever, chills, sudation (nocturnal), headache and associated discomfort, abdominal or epigastric disorders, diarrhea with mucus and blood. Hepatosplenomegaly may be observed. There is a marked leukocytosis (up to 50,000) with severe eosinophilia (up to 90 per cent) and as there are slight pulmonary opacities one can compare this syndrome to tropical eosinophilia. Urticaria is noticeable and may aid the diagnosis.

As in the preceding forms the most important symptoms are the result of the oviposition which begins as soon as the second or third month after the infection. The eggs are laid in the large intestine, but some are also laid in the liver and a number of other organs.

There is a scale of increasing seriousness in intestinal cases, from the latent asymptomatic or paucisymptomatic cases, to acute, toxic forms causing rapid death. The picture of severe colitis with muco-sanguinous stools and serious general disorders is frequently observed. Hypertrophy of the liver and spleen develops rapidly; serious anemia sets in; and finally, often after many years, atrophic cirrhosis of the liver predominates with ascitis, collateral circulation, splenomegaly, and diarrhea.

The intestine has become fibrous, papillomatous and more or less ulcerated. Cachexia or complications cause the patient's death. If the illness begins in infancy, somatic and sexual infantilism can be observed.

Also noted are the frequent deposits of eggs in various organs: lymph nodes, myocardium, and particularly the central nervous system. At this stage, or even in the beginning of the disease various symptoms have been described: epilepsy, cerebral troubles, central blindness.

Prognosis

Japanese schistosomiasis is particularly dangerous because of the abundance of the eggs, their peculiar toxicity and also because of the massive character of the infection in the endemic spot. An early treatment and removal of the patient from the endemic center give very good chances of cure. In the state of cirrhosis the prognosis is grave. Secondary cancerizations are described. The prognosis of nervous lesions is serious.

Diagnosis

At the invasion stage it is not very easy, unless the endemicity is recognized. It can be helped by the deviation of the complement (Fairley) or by the intradermo reaction.

At the stage of oviposition, the diagnosis is easy. Sometimes in very advanced cases, eggs are rare in the stools and occasionally none can be seen.

Treatment: Various antimonials are the main therapeutic resource. Emetin hydrochlorid has also been advocated.

Prophylaxis

The prophylaxis of schistosomiasis is practically the same for the different forms of the affection. It presents one of the most important and one of the most delicate problems in tropical regions today. Contrary to many other diseases, schistosomiasis is not favorably influenced by economic progress. The exploitation of alluvial mineral deposits, the increase of cultivated land and of irrigation are mainly responsible for the universal progression of the disease, in the incidence and in the seriousness of the affection. This observation has been particularly clear in the Belgian Congo. Elsewhere, the persistency of schistosomiasis is due in part to particular beliefs and customs, such as ritual ablutions in Egypt, professional contacts: laborers in the rice fields and of boatmen, in China.

Schistosomiasis is essentially a rural affection. However, after the floods of the Yangtse in 1931 the urban population of Shanghai was struck, the transmitting mollusc having been dragged in the canals of the town. European citizens residing in the tropics are more frequently infected while bathing in the lakes, the rivers, and even in swimming pools. Gravel filters do not hold cercariae and quite often a swimming pool is polluted with molluscs situated up-stream or near the spring which feeds it.

The reservoir of virus is exclusively human for *S. haematobium* and *S. mansoni* (excepting a few monkeys). *S. japonicum* is very widespread, on the contary, among various animals both domesticated and wild.

Of all helminthiases, general prophylaxis of schistosomiasis is the most difficult to realize. Germ carriers are extremely numerous and hard to discover. Whereas every other helminthic parasite of man evolves in a single larva, one schistosoma egg produces hundreds of them. The treatment of the disease is also very long and often imperfect in results. Moreover, infestation is linked to bodily cleanliness, religious practices, and necesssities of domestic life, which cannot be easily modified.

Let us consider the three main elements of prophylaxis:

1. *To reduce the peril of human reservoir*, one must (a) build septic tanks, sewers etc. (b) Avoid pollution of waters by urine and feces. Inculcate among the people the importance of fecal peril, and also of the urinary peril, which is more difficult to understand. Education in school, with the help of films, etc. There lies the surest way of fighting schistosomiasis. (c) Diagnose and treat the worm carriers. In Egypt, for 10 million contaminated cases, one million only ask for treatment every year, in spite of an intensive national propaganda which has been going on for many decades.

All these points are particularly difficult to put in practice for *S. japonicum* in the Far East, as human feces are used there as fertilizer. Moreover, dogs, cats, cattle, buffalo and wild rodents pollute the waters and contaminate the molluscs. Furthermore, the number of subjects infected is so large that one cannot plan a mass treatment. The one measure which can, therefore, reasonably be recommended seems to be the aging of feces before they are used as fertilizer.

2. *The Transmitters:* The destruction of transmitting molluscs seems a rational procedure. This, however, is not easy. Even in highly infected zones, it is often difficult to find the resting places of the transmitting molluscs. Their ethology varies considerably from one species to the other and from one region to the other.

The destruction of the molluscs has been realized (a) through mechanical means: clearing of weeds, cleaning out of canals with harrows and nets, periodic draining. These are only imperfect means. The first only reduces the malacologic fauna. The last are entirely without effect, since aquatic molluscs, even the nonoperculated forms, can stand dryness for several months. The operculated molluscs (transmitters of *S. japonicum*) are even more definitely amphibious. (b) Through chemical agents: Copper sulphate at 1 to 50,000 or 1 to 100,000 has been recommended and extensively used to destroy the molluscs as well as to kill the cercariae.

Mozley recommends the use of malachite (natural copper carbonate) thinly sprayed. A concentration of 0.5 copper salt for 1 million of water would be enough to kill *Physopsis* and *Planorbis* in nature as well as in the laboratory. Luttermoser in Venezuela (1943) successfully utilized freshly slaked lime in irrigation canals with acid soil. A solution of 0.1 per cent of the product kills the molluscs and their eggs in less than a day. Canals remain without molluscs for six months after the application. It is, however, recommended that the application be made every three months.

Saponin extracted from the fruit of the *Balanites aegyptiaca* (Archibald, 1933) kills the molluscs and cercariae within twenty-four hours at a dilution of 1 to 10,000. Unfortunately it is also toxic for fishes. *Balanites manghainii* (Wager, 1936, South Africa) has the same effect.

3. *The protection of the healthy subject* is easy to realize when taken individually, but it is far less so from the social point of view. Drinking water must be chlorinated or must have been kept on hand in purified condition for forty-eight hours. In notoriously endemic zones, or suspect zones, one must bathe only in waters free from human contacts, or purified. The building and supervision of swimming pools is absolutely necessary.

8. OTHER TREMATODES

Numerous digenetic trematodes exist in the intestinal tract, sometimes in the pulmonary tract of man. Their eggs are easily recognized by the oval shape, the yellow or brown color of the shell and the existence at one of the poles of an operculum. It is sufficient to mention only those which are distinctly cosmopolitan: *Fasciola hepatica* and *Dicrocoelium dendriticum,* two trematodes of sheep which are fairly often met with in the biliary ducts of man in sheep breeding regions.* After remaining from nine to fifteen days in water the eggs burst open and a miracidium escapes which infects a mollusc. This latter produces cercariae, mobile in water. Their tail is monocercal (not bifurcated) and contrary to the furcocercal cercariae of schistosomes, they are transformed into small spherical cysts, called metacercariae which live a considerable time in the water or on wet grass. Animals become infected by swallowing metacercariae. In man the infection is generally unimportant and does not produce any intestinal or hepatic symptoms.

Other trematodes are more particularly encountered in hot regions. Certain kinds are common and cause serious pathologic disorders. These are: *Paragonimus westermani* in the lungs and *Clonorchis sinensis, Opistorchis felineus,* and *Fasciolopsis buski* in the intestines. Others are relatively frequent, as, for instance, *Gastrodiscoides hominis*, *Metagonimus yokogawai*, and *Heterophyes heterophyes*, while some have been met with only very exceptionally in man, as, for example, *Watsonius watsoni* and several *Echinostomatoidea*.

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* In Syria a disease known as "halzoun" (meaning suffocation) is due to the accidents caused by *Fasciola hepatica* worms attached to the upper respiratory canals after eating raw liver of goats and sheep.

It should be mentioned in this connection that nearly all the trematodes seem to be able to act as potential parasites of man. Their occasional presence in man, therefore, does not come as a surprise.

Let us examine successively these principal digenetic trematodes.

(A) PARAGONIMUS WESTERMANI

Definition: Paragonimiasis is caused by a trematode, *Paragonimus westermani* (Ringeri). The principal symptom is hemoptysis.

History: The parasite was first known from the Felidae, then in 1880 in man from Japan (Balz) and from China (Manson).

Geographic Distribution: This helminthiasis is peculiar to the Far East. Yet it has been met with in various other countries such as Brazil, Venezuela, and the Belgian Congo.

Etiology: Paragonimus westermani (superfamily of the Troglotrematodea) lives in cavities or cysts lined by fibrous walls which communicate with the bronchi. Of brown color and oval shape, it measures 8 to 12 mm. in length and 3.5 to 5 mm. in width. The two suckers are the same size (0.75 mm. in diameter). The oral sucker is in front, the ventral sucker in the middle of the body. The eggs have a flattened operculum and measure 80 to 120 μ by 50 to 60 μ. They are expectorated with the sputum or swallowed and ejected in the feces.

Transmission: The eggs are hatched after two or more weeks in water. The miracidium infects a mollusc (especially various species of the genus Melania). The microcercal cercariae, with very short tail and provided with a stylet in front, penetrate the viscera and the muscles of crayfish (Astacus sp.) or crabs (*Eliocheir sp.*, *Potamon sp.*, *Sesarma sp.* in the Far East; *Pseudothelphusa iturbei* in Venezuela) and are there transformed into metacercariae. The consumption of these infected crayfish and crabs results in the development in the definite host: man, tigers, wildcats, panthers, foxes, wolves, dogs, pigs, civets, mongoose, etc. The metacercariae are liberated after digestion by the duodenal juice. They then wander through the intestinal wall, the abdominal cavity, and finally end in the lungs.

The pollution of water through expectoration and fecal matter by the animal reservoir is, in all probability, much more important than by human reservoir.

Pathology: Although Paragonimus has been found in different tissues their normal habitat is the lungs. They are found in cysts connected with the bronchi, or even representing broncheoli. A mild purulent reaction is created and later a state of fibrosis. The eggs are eliminated by expectoration. A similar evolution is to be seen in the intestines with intestinal elimination of the eggs. Eggs which have not been evacuated but sucked into the lungs may cause the production of tubercles. Pulmonary sclerosis may develop. Parasitic cysts, bluish in color, are mainly subpleural.

Symptomatology: The symptoms are those of chronic bronchitis with brownish, rusty expectoration and sometimes real hemoptysis. The stethoscopic or radiologic examination may disclose zones of condensation but not supply a causal diagnosis.

The evolution is chronic and the general condition remains quite satisfactory. More unusual symptoms have been quoted, referring to other localizations of the worm: enteritis, cerebral disturbances, etc.

Prognosis: Is relatively good.

Diagnosis: Is based on the research on operculated eggs in expectorations or stools.

Treatment: Emetine seems to be the most active product, used in the normal ways and with the usual precautions (see section on Amebiasis). If necessary, try antimonial compounds.

(B) CLONORCHIS SINENSIS

Definition: Clonorchiasis consists essentially in hepatic sclerosis.

Geographic Distribution: This disease especially widespread in China and Japan also occurs in other countries of the Far East and the Pacific (Hawaiis).

Etiology: Clonorchis sinensis (superfamily of the Opisthorchoidea) lives in the biliary ducts, sometimes in the pancreatic duct. It is a lanceolate worm, flat and transparent, 10 to 25 mm. long by 3 to 5 mm. wide. The ventral sucker is slightly smaller than the front sucker and is placed at the posterior limit of the front quarter of the body. The oval eggs are operculated at one of the poles and show a slight projection of the shell at the other pole. They measure from 27 to 35 μ by 12 to 20 μ.

Transmission: The miracidiums infect molluscs of the genus *Bithynia* and *Melania*. The cercariae are lophocercal (monocercal tail provided with a membrane on its whole length). The metacercariae are encysted in the muscles of various kinds of fish (*Cyprinidae, Gobidae, Anabatidae,* and *Salmonidae*). Man and numerous animals (dogs and cats) become infected by partaking of raw, smoked, tinned or insufficiently cooked fish.

Pathology: Dilation, thickening, and epithelial proliferation of the biliary canals constitute the regular picture. A varying degree of cirrhosis may be present. The pancreas can also be affected and show similar lesions of the pancreatic duct.

Symptomatology: The symptoms may be practically nil or else appear as digestive troubles: diarrhea, hepatic hypertrophy, jaundice, and finally decline.

Prognosis: Is variable according to the intensity of the infection.

Diagnosis: Presumes the discovery of eggs in the stools or in the bile.

Treatment: The most favorable seems to be Gentian Violet.

(C) OPISTORCHIS FELINEUS

Infestation by *Opistorchis felineus* (superfamily of the Opistorchoidea), trematode closely resembling the preceding one, also results in similar manifestations and lesions. This parasite is fairly cosmopolitan and well known in Germany, Russia, Indo China, and the Philippines.

(D) FASCIOLOPSIS BUSKI

Fasciolopsis buski (superfamily of the Fascioloidea) resembles the *Fasciola hepatica* because of its large size (20 to 75 mm. long by 8 to 20 mm. wide and 0.5 to 3 mm. thick), identical appearance of its eggs, its cycle in the mollusc (*Planorbis, Segmentina, Gyraulus*), and the encystment of its metacercariae on aquatic plants. It is a parasite which is frequently found in man and pig in China, Formosa, Indo-China, Borneo, Sumatra, Siam, and Bengal. Dogs also seem to be susceptible to a certain degree. Man becomes infected especially by consuming water nuts (*Eliocharis tuberosa*) on which metacercariae are attached. The worms fix themselves on the walls of the duodenum and the jejunum. There they cause irritation, ulcerations, and hemorrhage, even abscesses. In heavy infestations, toxic symptoms, edema of the face, of the abdominal walls and lower limbs can be observed. Ascitis frequently develops and death can occur as a result of the condition. Prognosis is very serious in advanced cases. Treatment with Caprokol or hexylresorcinol (0.4 Gm. under 7 years, 1 Gm. above 13 years) seems the easiest to bear and the most efficacious (McCoy and Chu, 1937).

(E) GASTRODISCOIDES HOMINIS

Gastrodiscoides (*Gastrodiscus*) *hominis* (superfamily of the Paramphistomatoidea) is fairly common in Assam and Cochin China. The pig constitutes the most important reservoir of the parasite. This worm measures from 4 to 5 mm. by 6 to 10 mm. It is pyriform, the front part being conical and the back part disc-shaped. The eggs are 150 μ by 60 to 70 μ. The cycle has not been established yet. *Gastrodiscoides hominis* is localized in the caecum and the ascending colon and can cause mucous diarrhea. It is susceptible to tetrachlorethylene.

(F) METAGONIMUS YOKOGAWAI

Metagonimiasis is frequent in Japan, China, Siberia, and the Balkans. It has also been reported in Spain. *Metagonimus yokogawai* (superfamily Heterophyoidea) is a parasite of the small intestine. It measures only 1 to 3 mm. by 0.4 to 0.75 mm., the ventral sucker being placed toward the middle of the body. The eggs measure from 25 to 30 μ by 15 to 20 μ. The miracidium does not free itself until after the ingestion of the egg by the first intermediate host, the mollusc (Melania). The cercariae is lophocercal. The second intermediate host is a fish. Numerous fish-eating animals, especially the pelican, serve as reservoirs, besides man. The symptoms are those of slight diarrhea. Prognosis is favorable.

Tetrachlorethylene (see Ancylostomiasis) constitutes an efficacious treatment.

(G) HETEROPHYES HETEROPHYES

This small trematode (it measures only 1 to 2 mm. by 0.3 to 0.4 mm.) belongs to the superfamily of Heterophyoidea. Closely related to *Metagonimus yokogawai*, the eggs are not distinguishable and they also are to be found in the small intestine. The symptoms, prognosis, and treatment are also identical. Heterophyasis is common in Egypt. Foci have been discovered in Japan, Korea, China, Formosa, and the Philippines.

(H) WATSONIUS WATSONI

This trematode has been found only once in man (black from Nigeria) who died from profuse diarrhea. The worms were very numerous on the walls of the duodenum and jejunum. The worm has been discovered in several Asiatic and African monkeys. *Watsonius watsoni* (superfamily of Paramphistomatoidea) is pyriform. The oral sucker is buried in the foremost extremity of the body. The ventral sucker is posterior. It measures from 8 to 10 mm. in length by 4 to 5 mm. in width and is from 4 to 5 mm. thick. The eggs are large (120 to 130 μ by 75 to 80 μ). The cycle is unknown and the infection probably occurs by the ingestion of metacercariae encysted on aquatic plants.

(I) VARIOUS ECHINOSTOMATOIDEA

Echinostoma ilocanum in the Philippines, *E. lindoensis* at Celebes, *Paryphostomum sufrartyfex* in Assam are the known species. The cycle of the first two trematodes is known. The first intermediate host is a mollusc (Anisus, Gyraulus), the second intermediate host is another mollusc (Viviparus or Corbicula, the latter being a bivalve). The consumption of raw molluscs infects man and dog. The worms are lanceolate (2.5 to 6.5 mm. long, by 1 mm. wide). The eggs measure 80 to 120 μ by 60 to 70 μ.

9. CESTODES

Most Cestodes of man, parasitic during their sexual phase (*Taenia*, *Botriocephalus*), or in their larval phase (*Echinococcus*, *Cysticercus* and the very rare *Coenurus*), are cosmopolitan and we may refer to parasitologic treatises.

Hymenolepis nana appears more frequently in hot countries, and it has an important pathogenic role due to its capacity for auto-infection. Its oval eggs are easily recognizable in excrements with their external shell of 40 to 45 μ diameter and internal shell of 20 to 30 μ; also by its triple pairs of embryonic claws.

Treatment employs Gentian Violet and hexylresorcinol.

Acranil, a substance similar to atabrin, has been prescribed against Taenia. A high dose seems necessary.

Cysticercosis is more prevalent in the tropics. Usually unobtrusive, it seems to provoke grave disorders only in certain localizations (brain, heart).

Sparganosis due to the presence of *Diphyllobothrium* larvae has been observed in Japan, the Congo and Indo-China. Ocular Sparganosis is frequent in this last country.

Chapter VI

SKIN DISEASES

1. LEPROSY*

DEFINITION: A very chronic infection caused by *Mycobacterium leprae* or Hansen's bacillus, localized principally on the skin and nerves. The disease has thus a dermatologic and neurologic appearance in which sometimes the one, sometimes the other predominates. It is transmitted by contact.

HISTORY

Although probably of very ancient origin in Egypt and the East, leprosy is not readily recognized in the records of the pre-Christian era. The "Carath" of the Bible is not easily identified. Greek science, which is the most accessible to us because of the clearness of language and identical ways of thought, does not appear to have recognized this disease until relatively late. It probably did not spread to the Mediterranean countries until after the Roman campaigns in Asia and Egypt. In fact, it is only at the beginning of the Christian era that we find the first indisputable description of what was then called elephantiasis, leprosy alluding to other skin diseases (Celse, Aretée, etc.). Leprosy followed the expansion of the Roman Empire westwards, subsequently, commerce, Saracen and Moor invasions, and finally the Crusades favoring the endemic. From the tenth and eleventh centuries the endemic had taken a great development and from the twelfth to fourteenth attained its climax. Civil and religious authorities became uneasy and isolation was enforced in numerous leprosariums (at least 42 in Belgium). Then the tide subsided and in the sixteenth century leprosy had practically disappeared from western Europe. The cause of this regression has been the subject of numerous discussions: the effect of isolation, natural selection, the disappearance of lepers during the great epidemics of plague in the fourteenth century, improvement in the standard of living have been cited. It is still, however, an unsolved problem.

Infected much later and for centuries having known extreme difficulty of existence, the countries of northern Europe were also the last to rid themselves of the malady which is only now being exterminated. It was in Norway in 1847 that Danielssen and Boeck definitely described the disease and it was also there that A. Hansen discovered the bacillus (1871–1873). This fact again gave first place to the theory of contagion and inspired modern prophylaxis, which was studied in a series of international conferences (Berlin 1897, Bergen 1909, Strasbourg 1923, Cairo 1938). Colonial expansion of the nineteenth century has given new interest to the study of leprosy.

GEOGRAPHIC DISTRIBUTION

The disease is entirely cosmopolitan but is rare in countries with progressive hygiene. In northern Europe leprosy is gradually dying out, new cases being very rare (Scandinavian Peninsula, Baltic provinces). Russia is a center of minor importance, at least in Europe. Western and central Europe are practically exempt, although here and there new cases develop through contact with returning colonials or immigrants (London, Paris, etc.). Southern Europe, especially Spain and the Balkans, has a certain endemicity. All of Asia is infected. Countries like India and China are said each to have a million cases (2 per thousand). Africa has, in general, a still higher index of about, or even over, 10 per thousand (Nigeria, Congo). In addition the general average in these countries does not reveal local situations where 20, 30, and 50 per thousand are noted. North America is scarcely affected. South America has an endemic index reaching from 1 to 3 per thousand (Colombia, Brazil). Argentina is also an endemic focus of some importance. Finally, Oceania is affected in all its tropical parts. Queensland is the only Australian province affected.

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* Synonym: Hansen's disease; French, Lèpre; German, Lepra.

In the Belgian Congo the forest regions (yearly rainfall at least 1,600 mm.) are more affected than the dry regions of the savannah.

ETIOLOGY

The *Mycobacterium leprae* has the form of a small straight or slightly curved rod, varying in size (1.5 to 6 μ, by 0.2 to 0.3 μ). It resists the acid-alcohol test, a little less though than Koch's bacillus, and is Gram-positive, nonmotile, nonsporing. Staining may be even or granulous. Contrary to the tubercle bacillus it has been neither perfectly cultivated nor inoculated in animals. The latter fact prevents the verification of cultures obtained by different experimenters which are sometimes of diphteroid appearance, sometimes acid fast and chromogenic.

Hansen's bacillus is readily distinguished from Koch's bacillus by its location: skin and nerves (where the tubercle germ is rarely encountered), and sometimes also by its abundance in these tissues where they are found in heaps or "bundles of cigars." The formation in globi is special to leprosy. By this we mean spheric or cylindric acid-fast masses formed by numerous bacilli agglomerated by amorphous matter to such an extent that the individual bacilli are no longer discernible. In certain cases (expectoration, for example) only the culture or inoculation of animals enables us to distinguish leprosy from tuberculosis which may evidently coexist.

The leprosy bacillus resembles the *Mycobacterium leprae murium* (Stephansky's bacillus), the agent of rat leprosy, a common disease of the wild rat inoculated in the white rat and hamster. In the Malayan Archipelago a nodular leprosy of the buffalo is found, caused by an acid-fast bacillus (Lobel).

It must be remembered that on the skin, in the nasal mucus, the auditory canal, on the most diverse objects there are acid-fast nonpathogenic bacilli which may be a source of error in the course of microscopic examinations.

TRANSMISSION

The disease appears to be transmitted only from man to man and by direct contact. Epidemiologic observations made in diverse localized centers (Island of Oesel in the Baltic, Memel, etc.) show the slow progress of the endemic, beginning with a known case brought to observation. Epidemiologic investigations made in all countries show frequence of contact as the probable source of the disease. The proof of contagion resides also in the rare positive inoculations; in particular is to be noted a case observed by Marchoux in Paris, a nonendemic region, where an interne was infected during a biopsy made on a leper. Very striking also are the rather rare cases observed of lepers settling in nonendemic countries (France, Great Britain) and contaminating relatives, etc.

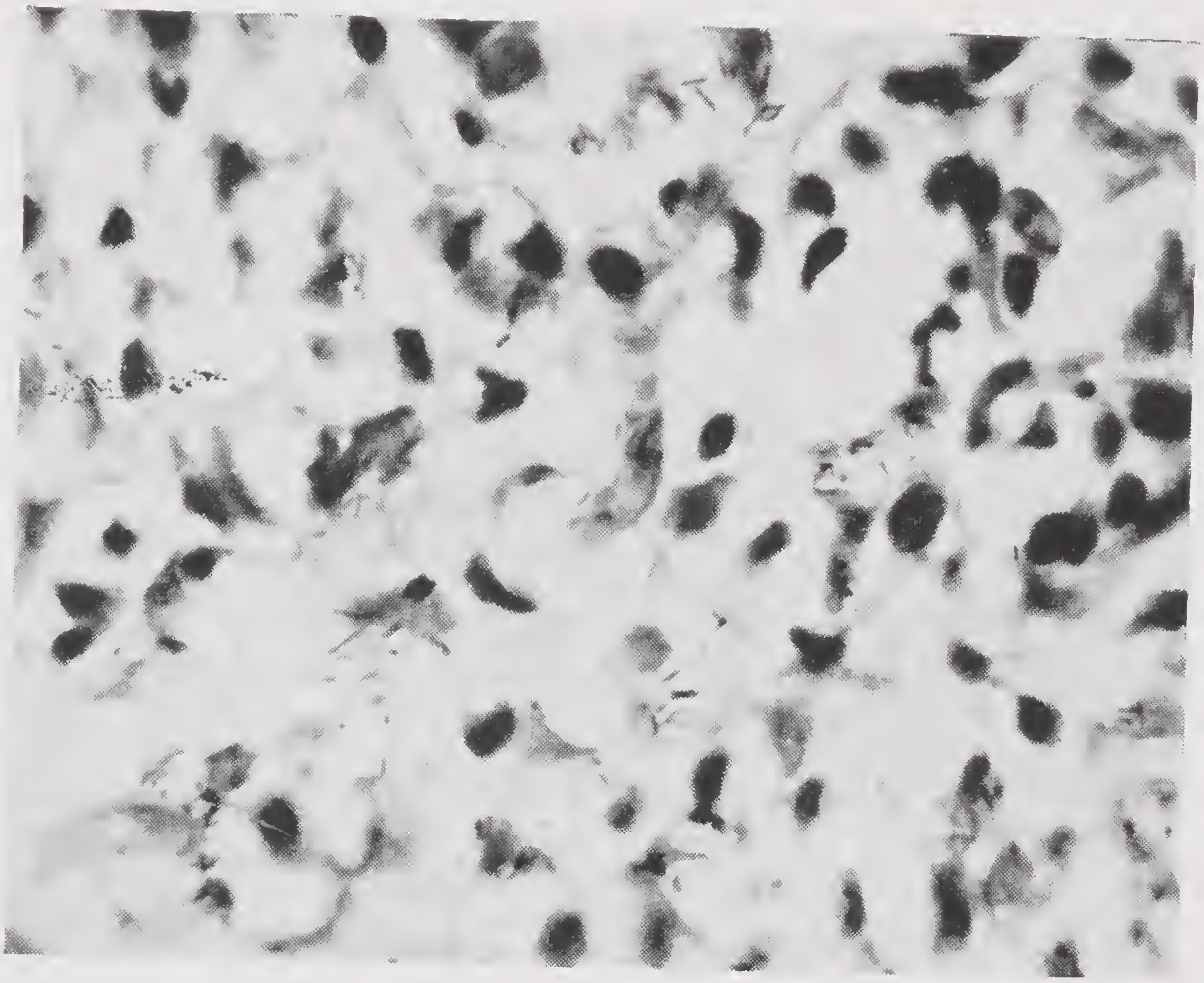

FIG. 51
Lepra bacilli seen in a section of a leproma (coll. Tropical Institute, Antwerp)

Although the contagion is considered a proved fact, it is not always easily achieved. It is certain also that the danger of contagion is all the greater as the leper excretes more bacilli. Cases with few bacilli are weak or not contagious. Elimination of bacilli is made chiefly by nasal-oral secretions, in addition to the discharge of open bacilliferous skin lesions. No doubt the penetration of the bacillus utilizes slight excoriations and occurs especially in open parts. Common itch, pyodermitis, etc., may represent an entry.

Although the sperm may be bacilliferous, the role of sexual relations is not considered as more important than common contact (rarity of conjugal infection). There is no congenital transplacentary transmission (sometimes erroneously called hereditary). Experience shows that the isolation of children as soon as possible after birth saves them from the disease. On the other hand, the child is either bodily or socially very sensitive and, like tuberculosis, leprosy is a family malady. The adult is less susceptible and conjugal contagion is rare. He may nevertheless be a victim of contagion as the example of numerous Europeans becoming infected in tropical lands shows.

We note sometimes that some of these patients do not seem to have been seriously exposed and we wonder whether certain persons, even adults, are not especially sensitive. In most countries more men than women are affected. The part played by food as a favoring element is not definitely established. We may believe, however, that everything that weakens the organism favors the development of the germ, which also applies to illnesses that weaken the patient. The direct active part played by fish (poorly preserved) and certain vegetables (Colocase) has not been proved.

General hygiene is an essential factor. Experience shows that leprosy is uncommon in civilized countries.

Finally, climate seems to have an influence, which, however, has not been made clear: in the Congo, Sudan, Nigeria, India, leprosy rages in regions where the rainfall is heavy (Rogers).

The hygienist distinguishes cases of open leprosy (excretion of bacilli) and cases of closed leprosy. The examination of nasal mucus is the surest method of establishing the excretion of bacilli. We shall see further on that the great majority of cases of the lepromatous form belong to the first category, while cases of neural leprosy are generally closed cases. It must be borne in mind, however, that they may sometimes also excrete germs in the course of bacillemia. The demonstration of their full harmlessness would be very important, for in certain countries (i.e., the Congo) they represent 80–90 per cent of the cases. Bacteriologic and epidemiologic observations tend to consider them of little danger.

PATHOGENESIS

It is possible that certain humans are refractory to the Hansen bacillus. These fortunate beings do not interest practical medicine. On the other hand, we sometimes observe cases called latent where the infection is confined to the presence of bacilli in the lymph nodes. Here, however, we must note that on account of the slow development of the disease such patients should be under observation for years before the latency be proved.

Besides, in leprosy we cannot dispose of a reaction of sensibility comparable to tuberculin, and on this account the study of its latency is not easy.

One degree higher in the scale of seriousness are cases, frequent in certain countries, in the Congo for example, called abortive or nonevolutive. Here we may see the real symptoms (spots, for example) remaining stationary for years or even regressing spontaneously. Such cases scarcely demand medical intervention, observation and good hygiene being sufficient.

The true disease begins with the form called nervous or neural (abbreviation: N.), paucibacillary, an appanage of resistant patients. Here the development of the bacillus in the skin is limited, arousing an energetic cellular reaction (spots). The nerve endings seem less able to defend themselves and are invaded by the germ, which finally reaches the nerves.

The cellular reaction in the nerves (interstitial neuritis) leads to undeniable functional disorders which constitute the seriousness of this form, formerly very correctly called maculoanesthetic. Tested by an antigen composed of dead bacteria extracted from leproma, such patients react by producing papulae (positive lepromin reaction). They are, like normal men, normergic or even hyperergic.* The type of histologic reaction, especially in the skin, often takes on a tuberculous appearance (epitheloid and Langhans cells), usually without caseation.

Contrary to the paucibacillary form, we have the multibacillary form, also called lepromatous, on account of the existence in these cases of nodules or lepromas (abbreviation: L.). Here the patient's resistance is weak. Tested by lepromin he frequently responds negatively (anergia) and the bacteria multiply and reach a number which is not attained in any other microbian infection. By continuity or by bacteriemia the neighboring mucous membranes (nose, eyes, etc.) and the deep seated organs (testicles, liver, spleen) are attacked. The nerves are affected also but react only later and then with the ordinary symptoms of leprous neuritis (this is complete or mixed leprosy; abbreviation: L.-N.). Sometimes certain patients finally acquire sufficient resistance in the skin to rid themselves completely of the cutaneous infection and retain only the nervous phenomena (these are secondary N. cases). There is a certain contrast between intense cutaneous infection and nervous symptoms. The appearance of the latter is ordinarily followed by a certain improvement in the cutaneous lesions. It should be noted that the contrary may also occur and an N. patient may show more and more bacteria and enter the L. form (this would be an N. L. case). Anergy to lepromin is often noted in these patients.

It is important to know that the long development of leprosy is accompanied by few general toxi-infectious phenomena. The patient goes about for years, capable of strenuous physical effort. Slowly, however, his health changes and his life is in danger, especially in the L. form. We observe, in the course of this slow evolution, reactionary phases, sometimes general with toxi-infectious syndromes, sometimes local with swelling of cutaneous lesions or exacerbation of neuritic phenomena. Further on we shall again speak of these "leprous reactions."

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* Positive reactions have been noted on patients in nonendemic districts.

PATHOLOGY

Hansen's bacillus is a parasite of cells. It may be considered as a parasite of the reticulo-endothelial system "sensu lato" (including the fibrocytes and vascular endothelium). The organism reacts by a specific granuloma in which intervene simultaneously infiltrative and proliferative cellular elements, the latter predominating. Among the former we must note the almost complete absence of polynuclear cells. Cellular reaction appears in three principal forms, most easily observed in the skin, but also in the nerves, the viscera, etc.

1. Infiltration composed of small cells: lymphocytes, small hystiocytes, plasmocytes, often spread along the vascular nervous dermic plexus. The bacilli are at times rare, at others plentiful. The first eventuality is seen in incipient or quiescent N. lesions, the second in incipient lepromatous lesions. The body reaction is usually normergic (lepromin test).*
2. Tuberculoid granuloma, made up of typical epitheloid cells, of giant cells of the Langhans type, of lymphocytes and other small cells, often in small numbers (this is the reason for the light chromophilia of the infiltration). The bacilli are almost always rare. These infiltrations are seen in the raised active neural macules, rarely in the nerves which may in this case show caseation. The lepromine test often shows hyperergia.
3. Lepromatous granuloma, characterized by abundance of Virchow cells (foamy cells, Schaumzellen) with spongy cytoplasm, and by the presence of many bacilli. The leprous cell does not differ greatly from the epitheloid cell: a large cell containing one, or more, rarely several vesicular nuclei with a vacuolated cytoplasm. These vacuoles contain a lipoidic and soudanophilic substance.

The lepromin test is usually negative.

The leprous infiltrations have a very feeble tendency to caseation, but may develop

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* *Lepromin test. Mitsuda test.* A bacillary emulsion extracted from lepromas and sterilized after one hour of boiling has been used in intradermal injections of 0.1 cc. There is an immediate and delayed reaction (from one to three weeks) with the following responses:

	Immediate	Delayed
Lepromatous	−	−
Nervous	+	+
Tuberculoid	++	++
Normal subjects (nonendemic regions)	−	+ (50 per cent of the cases)
Tuberculosis	+	−

L. and N. subjects sometimes react abnormally. This fact would have a significance for the prognosis. Purified filtrates have been used without much benefit. The delayed action is the most valuable. Because of its nodular character, it is easy to read in dark colored subjects. In central Africa the majority of the subjects have a delayed positive reaction.

in sclerosis. In the nerves, the fibers are put out of action in the beginning by the density of the infiltration, later by the sclerosis which finally transforms entire bundles of nerve fibers into fibrous blocs.

In cases of neural leprosy we note an infiltration of small, round cells and lesions of fibers, demyelinization, fatty soudanophilic degeneration. In old cases sclerosis predominates. The bacilli are more easily seen than in the skin.

Tuberculoid structures may also be observed. In lepromatous cases the nerves are seriously attacked by the bacilli, sometimes with little histologic reaction (and by this fact there are few clinical phenomena), sometimes by true leproma, and later by sclerosis.

BIOCHEMISTRY

A pronounced disturbance of the protein balance of the plasma is observed in serious leprosy, especially the lepromatous. The total amount of protein is increased and more especially so the globulines. The serine globuline quotient tends toward unity. A series of aspecific plasmatic reactions are therefore used whose value is prognostic rather than diagnostic.

A relatively high number of false reactions of Bordet-Wassermann also seem to follow. American serologists who studied the question in 1936 estimate these errors at 50 per cent. In the Congo the frequency of yaws in the antecedents makes it difficult to appreciate this fact. The hematology is normal, or without characteristics. In resistant subjects the N. form shows lymphocytosis, which is absent in the nodulary form.

SYMPTOMATOLOGY

The period of incubation is estimated at about two to three years but may be much longer. Often leprosy contracted during infancy appears at adolescence.

Prodromes. All kinds of prodromes, general and local, have been described. It is not easy to know which among them are leprous and which belong to intercurrent illnesses eventually favoring the development of leprosy.

First Symptoms: There is no primary lesion with its anatomo-clinical or serologic characteristics as in syphilis or tuberculosis. But naturally there is a first lesion or a first symptom and its appearance varies. Frequently, and especially in Central Africa, one or several macules constitute the first sign. One single macule may remain as such for years, but in this case it is nonevolutive leprosy.

Various writers of the Far East have described, especially in children, small, hazy, multiple spots whose clinical and bacteriologic diagnosis is difficult. Here the history (contact) or the evolution will confirm suspicions. These cases may easily become lepromatous, children being seriously infected (Chiyuto, Cochrane). A beginning of neuritis is also possible:

anesthesia, with consecutive burns, etc. Sometimes the most peripheral fibers only are affected and partial paralysis of the face, for example (Wayson), or very light anesthesia in places may follow. An onset by lepromatous bacilliferous infiltrations is also possible.

Sticker's old theory of an endonasal beginning is no longer considered as corresponding to current facts.

Period of active infection: The neural and the lepromatous forms should be considered separately. It seems to us that we say too easily that all forms of leprosy are mixed. If we mean by this that in each case lesions are found on the skin and others on the nerves, we agree. But we have insisted sufficiently on the fact that the difference between the two forms is quite another matter: bacteriologically (scarcity or abundance of bacilli); histologically (tuberculoid or lepromatous infiltrations); immunologically (reaction positive or negative to lepromine); even prognostically (slight or real "quoad vitam" danger). No doubt we can see an N. case becoming L., but in many cases this does not occur: the patient, who owing to constitutional or acquired dispositions is N., will remain so all his life. It seems to us that there is a greater difference between N. and L. lepers than between a tuberculous case of first infection with its tendency to general dissemination and its affected lymph nodes, and a case of tuberculosis of the lungs in an adult with its absence of glandular extension and its particularly local progress. As to L. N. cases they are always L. cases.

Neural Leprosy

Neural, maculo-anesthetic, maculo nervous, N. The two essential symptoms are spots plus nerve troubles.

Neural macules: They are erythematopigmentary, the discoloration being in the colored race always a depigmentation (coppery appearance). In the white race the skin is red, brownish red, sometimes entirely white (vitiligo gravior). The macules are sometimes flat (simple neural spots Ns), sometimes infiltrated, raised (tuberculoid spots NT or Nt, major or minor tuberculoid according to whether the swelling is total or, on the contrary, composed of small papulous elements). The tendency to radial extension is notable, the center possibly resuming a normal appearance (circinated element). The number varies from one to many. The irregular localization affects the extension surface of the limbs (back, buttocks, thighs, arms), frequently the face, seldom the soles of the feet and the palms, very rarely the scalp. These spots often show nervous disorders: (a) superficial anesthesia (rare in the Congo); (b) thermo analgesia; (c) anidrose (70 per cent of the cases); (d) incomplete reaction to histamine, lack of extensive erythema; (e) sometimes falling out of hair and down; (f) thickening of local nerve fibers (very rare in the Congo). The bacteriologic examination is feebly positive or negative.

Neuritic symptoms: Here it is a question of neuritis of the important nerves, most frequently of ascendent origin. The reaction to the presence of bacilli is at first infiltrative, later fibrous. The result is a progressive change in the functions of the peripheral nerve fibers. This neuritis may result in regular or nodulary thickenings of the nerves and, rarely, cold abscesses of the nerves. It is especially recognizable by functional troubles.

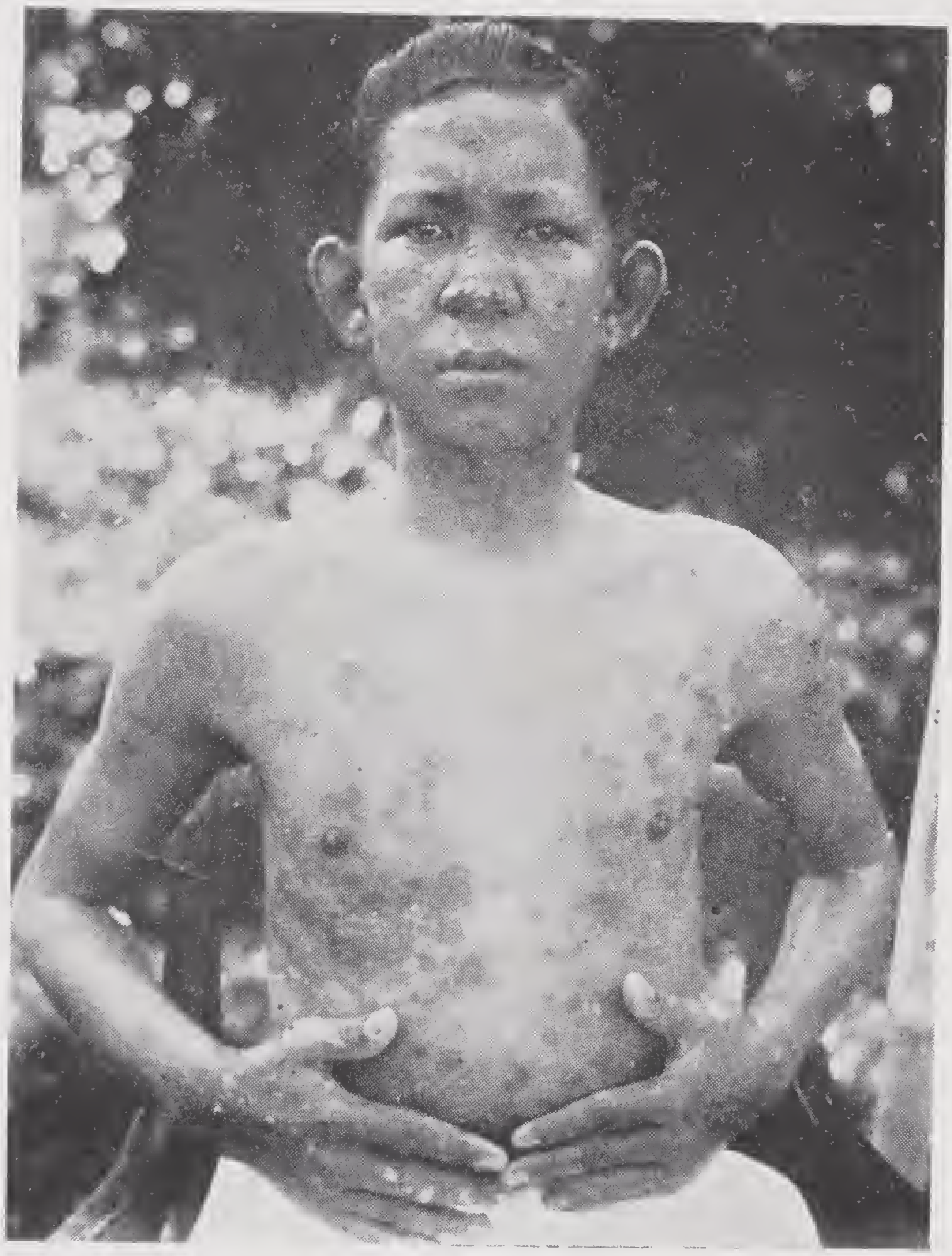

FIG. 52. LEPRA
L. form with macules on the torso and infiltration with small nodules on the face (Courtesy Dr. E. P. Snijders, Indisch Instituut, Amsterdam)

Sensibility: Subjectively, paresthesias and neuralgias are often observed. The latter may be very painful especially in the course of reaction when the nerve is strangled in its osteofibrous sheath. Sensibility is affected in various ways (touch, pain, heat) and the patient often burns himself. The area of anesthesia is of varied extension; elongated according to the distribution of the nerves, it is especially distal, and ends by affecting almost all the extremities, rarely going above the elbow or knee. Sensitiveness to pressure and muscular sensation are rarely affected.

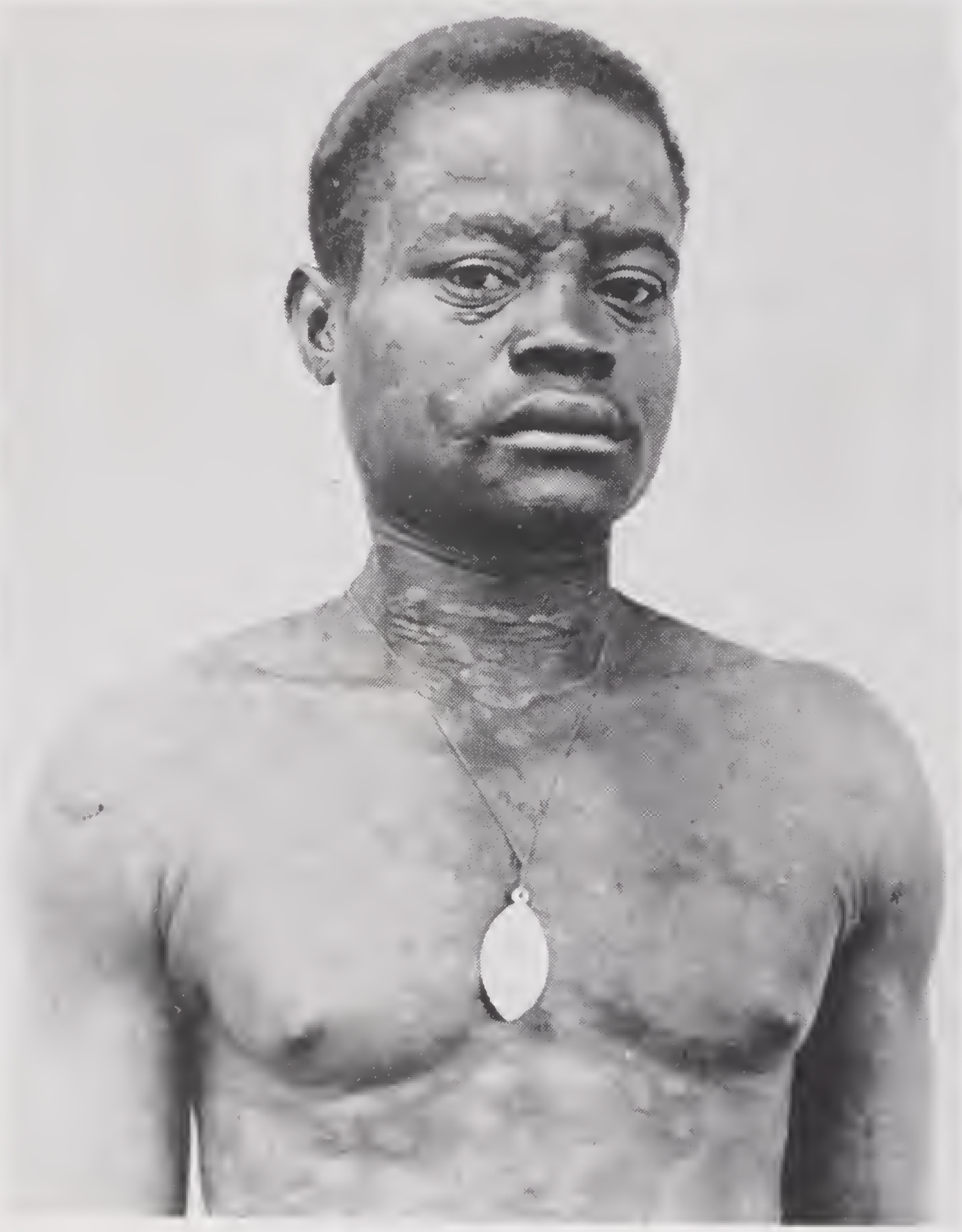

Fig. 53. Lepra
Tuberculoid Macules, Congo (coll. Tropical Institute, Antwerp)

Trophic Disorders: Vasomotor symptoms: cyanosis and chills are frequent. The dry, keratinous skin often shows blisters, sometimes superficial, sometimes deep (lazarine leprosy). They are frequently located on the elbow and knee (parchment-like scars).

Ulcers are common, facilitated by traumatisms (especially of the feet) and assuming particularly the appearance of "mal perforant."

The bones and the articulations are the seat of the process of resorption. Whitlows and superadded abscesses aggravate the case and end in mutilations or acroteric lesions which finally transform the limbs into stumps.

Motor Disorders: The muscles of the limbs are atrophied. The atrophy of the thenar and hypothenar eminences follows, also that of the interosseous muscles of the fingers (claw hands), dropping foot (lesion of the external popliteal nerve), and facial paralysis with lagothalmia and changes of the cornea, anomalies of the facial muscular structure and of the lips (epiphora, salivation, "antonine leprosy").

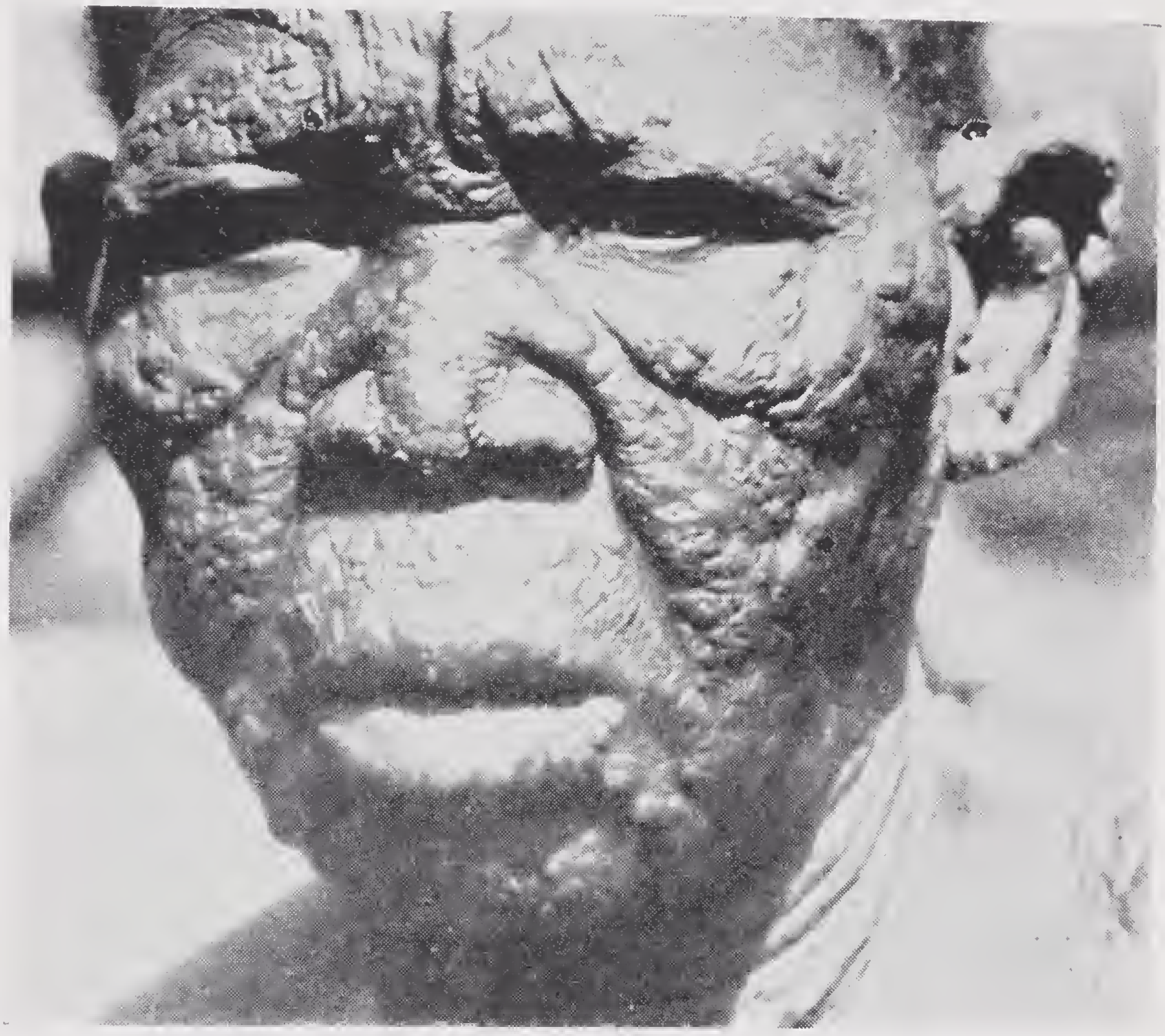

FIG. 54. LEPRA

L. form with macules on the torso and infiltration with small nodules on the face Antwerp)

Lepromatous Leprosy

On the skin we may observe: (a) *Macules,* often small and numerous, congestive, with poorly outlined edges of reddish brown color, becoming brown on vitropression (in white people), localized infiltrations, resembling the macules but with more distinct infiltrations. (b) *Diffused infiltrations*, in which the shiny skin, moderately thick, may, in colored races, attract little attention. In other cases the exaggeration of the markings of the skin is accentuated. After congestive periods, the resolution often gives to the skin an appearance of crushed tissue-paper (pseudo-ichthyosis). (c) *Nodules or lepromas:* solid nodules, anesthesic, dermic or more rarely hypo-dermic, sessile, more rarely pedunculated, of brown or violet tint in clear skins, almost normal in blacks. They are found especially on the face (edge of ears), on the wrists and back of hands, on the buttocks, etc. Combined with infiltrations, the nodules give the so-called leonine appearance of the face. Alopecia of the eye-brows is common, though, with the exception of Japan, that of the scalp is rare. (d) *Ulcers:* without characteristics, either traumatic, or neuritic, or more seldom following melting of the infiltration.

On the nose, we observe quite regularly ulcerous-scabous rhinitis causing the perforation of the cartilages and collapse of the tip.

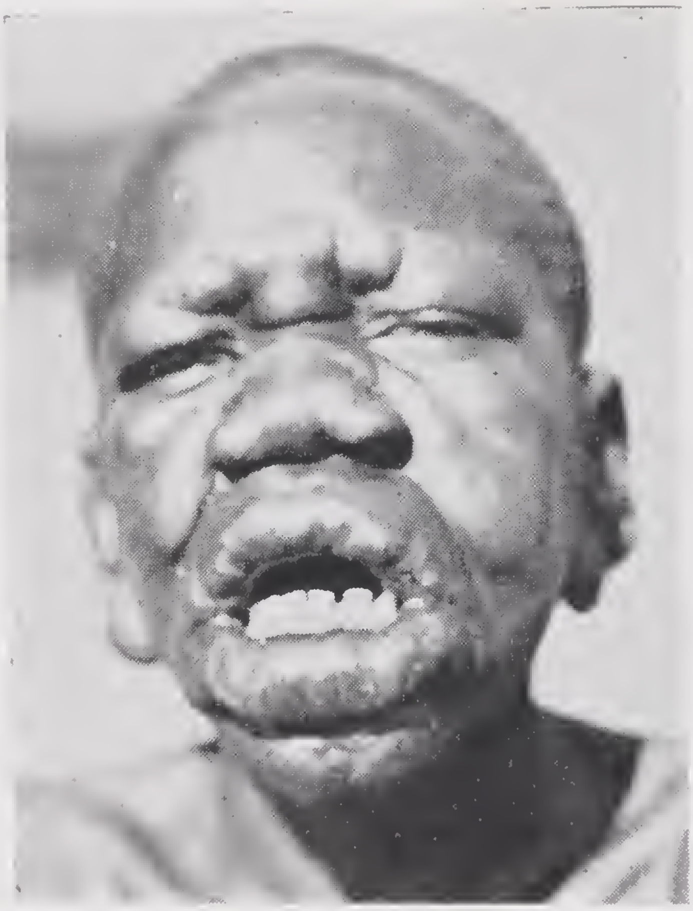

FIG. 55. LEPRA
L. case from the Congo (coll. Tropical Institute, Antwerp)

In the mouth, nodules of the palate and the tongue are common. In the pharynx and the larynx, leprous infection sometimes spreads to the trachea. The larynx is often affected, causing hoarseness and crises of stenosis (very rare in the Congo).

The eye: Conjunctival keratitis and iritis are observed following the invasion of the face.

In the viscera: Though the viscera may show leprous infiltrations (by bacillemia), only the testicles show a recognizable orchitis and nodulation followed by sclerosis. Azoospermia and gynecomastia are observed.

In the nerves: Sometimes much later and sometimes with an appreciable improvement in cutaneous signs, the nerves are put out of use. The consequence is a disturbance analogous to that cited in nervous leprosy. These are L. N. (mixed leprosy cases) with an infinite variety of ulcers. atrophies, mutilations.

The general condition is variable; malaises, fever, etc., are not rare. Finally, a true leprous cachexia begins in L. cases. However, most of the cases remain ambulant a long time, as leprous fever has few symptoms of malaise.

Leprous reaction: The slow course of the disease is interrupted now and then by sharp attacks or reactions. Their mechanism is not well understood: sensitization or bacillemia attacks. The reaction has general toxi-infectious symptoms of variable gravity and duration which may cause adynamia and the patient's death. There are also local symptoms: of swelling of existing lesions, nerve pains, appearance of new nodules which may sometimes be resolvant. Local reaction may have a weak general effect. The determinating causes of reaction are multiple and sometimes obscure: too active treatment, potassium iodide, intercurrent illnesses, including Jennerian vaccination, etc.

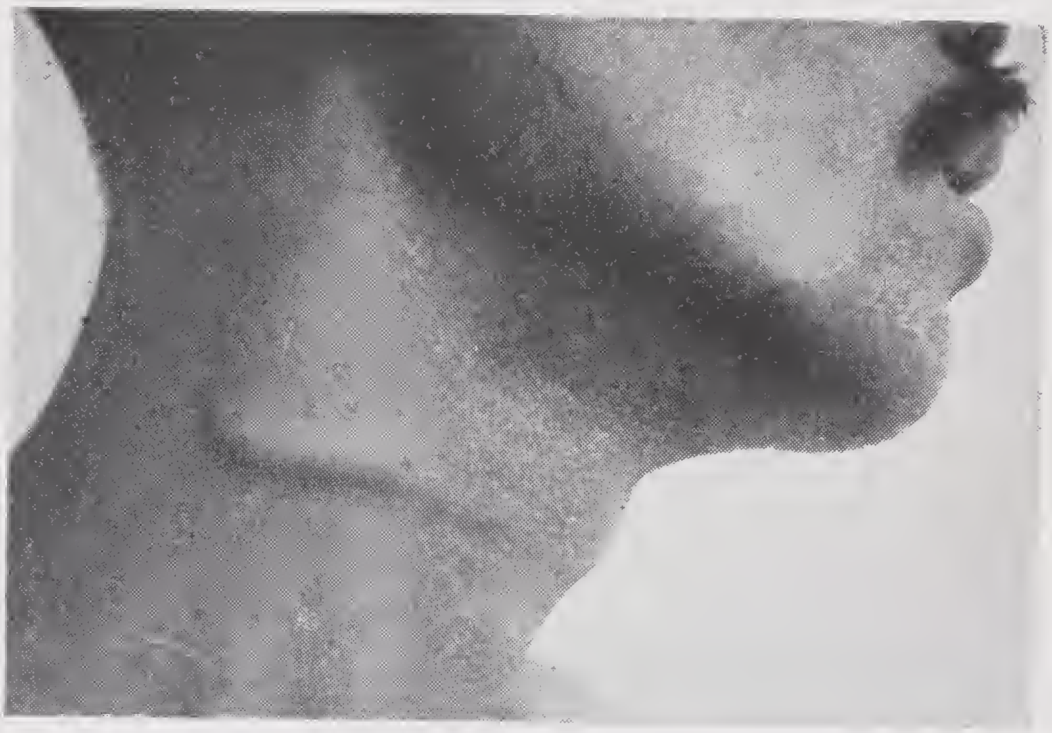

FIG. 56. LEPRA
Thickening of a neck nerve (courtesy Dr. E. P. Snijders, Indisch Instituut, Amsterdam)

The prognosis of the reaction is variable. In certain cases the patient may improve after having surmounted this test.

GENERAL PROGNOSIS

Except for nonevolutional cases, the functional prognosis of leprosy is serious. Two-thirds of our isolated Congo patients finally show serious mutilations. The vital prognosis, favorable in N. cases, is poor in L. cases, where survival rarely exceeds 10 years. The prognosis of N. T. cases is favorable; nevertheless, here and there they develop mutilations and quite exceptionally turn to the L. form. The reactions to lepromin and to blood sedimentation are of real prognostic value, the first in the long run, the second in following the evolution of the disease from week to week. Death often occurs through intercurrent illnesses (tuberculosis, pneumonia, infected wounds, nephritis or amyloid degeneration). Stenosis of the larynx may necessitate tracheotomy. Relapses after apparent cures are frequent.

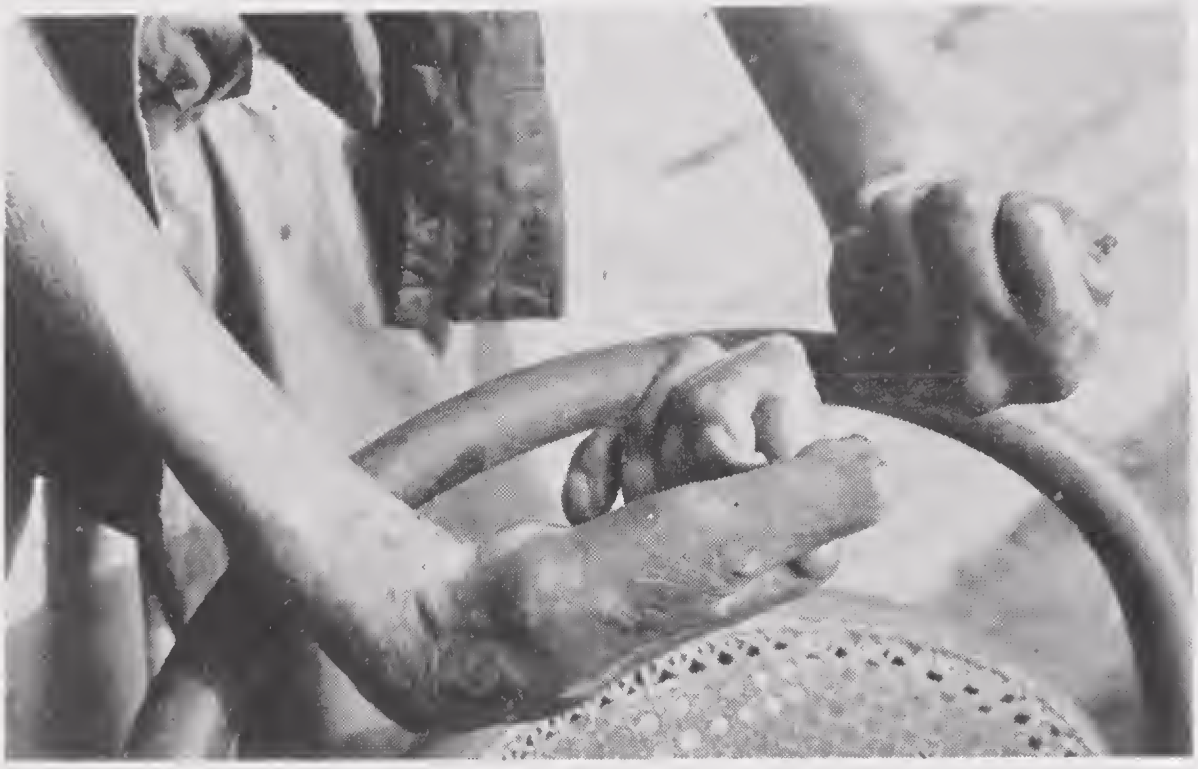

Fig. 57. Lepra

Claw hands, resorption and atrophy of the muscles (courtesy Dr. E. P. Snijders, Amsterdam)

DIAGNOSIS

The diagnosis of the L. form is made easy by the abundance of bacilli. Clinical confusion with a series of nodular dermatites is possible even in true lepromatous cases, but the distribution of the eruption is often typical (ears). The diffused lepromatous form may be really difficult to suspect in blacks where the color of the skin does not easily show it. These patients constitute a health problem, in the course of rapid examination made during a census of population. The wisest course is to keep leprosy and its atypical forms in mind and to make bacteriologic examinations in doubtful cases.

Diagnosis of the N. form may be either very easy or very difficult. The former case is indicated by the association of spots and neuritis, which cannot cause confusion. Isolated spots may be confused with psoriasis, (rare in colored patients, squamous and particularly localized on elbows, knees and scalp), with mycosis (more vesicular and squamous and typical under microscopic examination), with certain tardy macules of syphilis or yaws (history of the patient, seric reactions, trial treatment).

Vitiligo (leucodermia) can hardly be mistaken: history, absence of sensitive signs, extreme depigmentation.

A spot cannot be called leprous excepting with certain signs: (1) anesthesia or anidrosis. (2) thickened cutaneous nerves, and (3) bacilli found in the skin, the nasal mucosa and the glands. The diagnosis of cases which are neuritic only may be difficult also. It is possible to confuse them with syringomyelia but the latter shows radicular anesthesia and pyramidal signs, some cyphoscoliosis, and has neither swelling nor bacilli of the nerves. Raynaud's disease shows sphacelus but no anesthesia.

Bernhard's syndrome, neuritis of the outer femoral nerve, has only localized sensitive signs (outer surface of the thigh) and is resolutive.

Research for anesthesia: This is best made by blindfolding the patient and then touching different parts of his body, with a bit of cotton, which he must indicate correctly with his fingers.* Thus, superficial anesthesia to light contact may be found. Thermoanesthesia is found by comparing 2 test tubes containing cold and moderately hot water. Analgesia is evaluated by comparing 2 pin pricks in healthy and in suspected parts. Anidrosis is shown by having the patient make a physical effort after having brushed the spot and surrounding skin with tincture of iodine. After the exercise sprinkle the entire part with starch: the anidrotic spot remains white, the healthy skin showing a reaction to starch iodide (black). We can also give intradermic injections of pilocarpine of 1 per cent (0.1 cc.) in healthy and in suspected skin, using the same starch test. Histamine may also be used on fair-skinned patients: put a drop of solution, 1 per thousand, on the skin, pricking lightly, without bleeding. Remove the drop after a moment. The erythematic extension noted after fifteen to thirty seconds is made only in normally innervate skin.

Bacteriologic Diagnosis: It is necessary to look for the bacillus. In L. cases the finding is always strongly positive, often with packets or globi of bacilli. On the contrary, in N. cases, the research is often negative, or the bacilli observed are so rare that the observer is not very certain (possible confusion with nonpathogenic skin bacilli, etc., bacilli left on the skin, insufficient cleaning of slides). We reduce the latter causes of error by observing the following precautions in N. cases: (1) well cleaned instruments reserved for N. cases, (2) new slides or at least some left for a day in chromo-sulfuric solution, (3) careful cleaning of the skin. Under these conditions we do not exceed in N. cases 30–40 per cent of positive examinations and these are still very slightly so. We shall consider the microscopic examination of these patients more revealing as to the form of the disease than to the disease itself. Note the number of bacilli in 50 microscopic fields (immersion). Research is undertaken after Zielh-Neelsen staining:

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* The feet of natives having horny soles must be touched with a paper spill, cotton being too light.

1. In the skin, after incision (superficial) and scraping of the derm (the active area of the spots: lobes of ears, forehead, healthy skin).
2. In removed nasal mucosa.
3. In nasal mucus by swab (of great public health significance).
4. In the lymph by puncture of the lymph nodes.
5. In a thickened nerve (incision, longitudinal scraping).
6. In the centrifuged blood, bone marrow, liver (none of these in great use).

Histologic Diagnosis: May be useful. A distinct tuberculoid structure will help to strengthen the diagnosis. The lepromatous structure is pathognomonic but the bacteriologic examination suffices.

Serology has, up to the present, been of little use. The Bordet-Wassermann, independently from syphilis and yaws, is often positive.

CLASSIFICATION

Quantitative: We often mention L. or N., 1-2-3, according to the total seriousness of the symptoms.

Qualitative with associated quantitative indication (1-2-3). N. cases are divided into:

Ns. (neural with simple flat macules) 1-2-3.
Na. (nervous anesthetic or acroteric) 1-2-3.
NT. (nervous tuberculoid with fully raised macules) 1-2-3.
Nt. (nervous tuberculoid with micropapulous macules) 1-2-3.

We sometimes use the notation N. B.+ for neural cases with more bacilli than is usual for N. cases, and which appear to us to be developing into L. cases. L. cases are sufficiently described by the quantitative mention 1-2-3, according to the spreading of the lesions. We may, however, classify them as:

L., typical lepromatous.
Ld., diffused lepromatous without true lepromas.
Lm., lepromatous, macular.

L. cases with neuritic symptoms are marked LN. or, better, L.-Na., i.e., L. 3 Na. 1 or L. 2 Na. 3, etc. For example:

Ns. 3–Na. 1: numerous spots, light anesthesia of the extremities.

Ns. 2–Na. 3: macules and developed acroteric lesions.
Na. 1: anesthesia of the extremities, no macules.
Na. 3: acroteric lesions, no macules.[*]

TREATMENT

Leprosy is a chronic affection where the general treatment is very important: fresh air, exercise, good food, vitamins, calcitherapy, cleanliness and hygiene of the skin, including the use of chaulmoogra unguent, care of the teeth and the mouth. The maintenance of the psychic balance is of prime importance and with this in mind an occupation is the best distraction. The treatment of intercurrent illnesses, worms, malaria, syphilis is also necessary.

Specific Treatment: The only product having withstood experiments was, until quite recently, chaulmoogra oil. More recently, fairly promising trials made with different sulfones have been developed.

Oil of Chaulmoogra: Its esters and soaps:

1. Pharmacognosis: It is an oil of various tropical Flacourtiacea of which the most important commercially are *Hydnocarpus laurifolia* (*wightiana*) and *Hydnocarpus anthelmintica,* both from the Far East but grown in Africa. Local resources may be represented by Caloncoba in Africa, Carpotroche in America. These glycerides of "suigeneris" odor have a fusion point of 22 to 25 C., an iodine index of about 100, and more characteristically a strong rotatory power to the right on polarized light ($\alpha_D \pm 50^\circ - 60^\circ$). Chemically they are composed of glycerin and various fatty acids, some ordinary, others characterized by a pentenylic cycle of 5 atoms of carbon with one unsaturated link and an asymmetric atom. Hydnocarpic and chaulmoogric acid amount to 150 Gm. per Kg. of oil.

Strictly fresh oils must be used and their acidity must remain between 1.80 and 3 cc. of NaOH N/10 per Gm. of oil.

2. Pharmacodynamics: The oils irritate the digestive tube and often the tissues. Their toxicity is weak; in strong doses there are lesions of the kidneys, liver, blood. The soaps are more toxic by way of the veins.

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[*] Recently South American leprologists have proposed a classification in the three following forms:

	Bacilli	Lepromin Test	Histology	Evolution
1. Lepromatous	+++	−	Virchov's cells	Severe
2. Tuberculoid	+ rare	+ to ++	Tuberculoid cells	Mild
3. Aspecific	+ rare	+ or −	Nothing specific	Toward L. or T.

In fact, there is little difference. The tuberculoid form in the quiescent stage takes an aspecific aspect (flattening of the macules, histologic structure of common inflammation). Unfortunately it is among these subjects that the neurites develop. The classification in N. and L. seems to us satisfactory. Nothing differentiates T. from N.

Launoy considers the dose of mixed soaps limited to 1 mg. for 20 Gm. weight in mice (intravenous), while the oil is tolerated at the rate of 50 mg. (subcutaneous). Local resorption is slow and the treatment may accumulate fats with active acids in the animal.

3. Experimental therapeutics: The effect on rat: leprosy is rather weak. Chaulmoogra substances inhibit the growth of Koch's bacillus. Most probably the pentenylic cycles give these oils their special activity.

4. Human therapeutics: The oil seems superior to the esters and is certainly so to the soaps. This is in regard to a treatment continued for months, often years, with occasionally two to three weeks' rest. Injections are made in the muscles, rarely under the skin (using product of slight irritation, 0.5 cc. per area); oftener in the derma of lesions or in healthy skin. The dosage begins with 1 cc. and reaches 4-5-6 cc. once or twice a week with one intramuscular and one intradermal area. (Inject 0.1 cc. ten, twenty, or thirty times, at five to ten mm. spaces. The treated area receives no further treatment for one month.)

Injections in the veins are little used (emulsions of oil). The intradermic seem the best. Here also we need products causing little irritation, otherwise we observe small eschars. After one to three years the patient will have received 1 to 2 liters of the product.

Result: Light cases are frequently checked (N. cases). Moderate L. cases may improve but rarely be cured. Anglo Saxon observers seem more optimistic than we, perhaps because they often work in closed establishments and can assure a more regular treatment. Serious L. cases improve a little, ordinarily remaining bacillary. The prophylactic action (suppression of the germ) is not to be counted upon. A too brutal treatment may facilitate the appearance of "leprous reactions." This dictates an abstention and a prudent renewal of the treatment after the end of the reaction.

Sulfones: The following have been used with quite favorable results. The still recent experiments do not allow us to advise a definite posology.

(*a*) *Promine:* Sodium p.-p'-diaminodiphenylsulfone N.N' didextrose sulfonate is given in doses of 2 to 5 Gm. in daily intravenous injections, six days of the week. The treatment lasts several months with one day of rest, and a longer rest (two weeks) after four months. A careful examination of the patients is necessary, and in particular a blood analysis every fifteen days. Watch the kidneys. Notable improvements, probably cures, are related. The danger is always in regard to the blood. Under 4 million red globules, iron must be given and eventually gastrohepatic extracts. Phenomena of sensitization may be combated by desensitization beginning with 100 mg. of the product in the veins and increasing progressively.

Pite and Gemar (1946) give 5 Gm. a day intravenously during 21 consecutive days followed by a week's rest. The treatment is continued for more than four years.

(*b*) *Promizole:* 2-4′diamino-5 thiazolyl-phenylsulfone is given by the mouth in doses varying from 6, 10 and even 16 Gm. We begin with 4 Gm. and increase progressively. Eighty per cent of the elimination is made by the urine which may become reddish. Intoxication is less than by Promine, but the kidneys must be watched (albumin, blood, crystals), as well as the skin and the blood. The treatment lasts months with one day of rest weekly.

(*c*) *Diazone:* Disodium formaldehyde sulfoxylate-diamino diphenyl sulfone is given in doses of 330 mg. to 1 Gm. for six months and more. General remarks as for other sulfones.

Special Treatments:

Nose: If there are scabs and bacilli: weak alkaline douches of the nose, then a swab of diluted hydrogen peroxide and an antiseptic spraying. Promine unguent.

Eyes: Atropine in cases of iritis (except where there is a tendency to glaucoma), or better, collyrium of scopolamine.

Ulcers: Complete rest, surgical treatment of sequestra, amputation. Infiltration of chaulmoogra oil along the nerves.

Lepromes: Carbonic snow.

Spots: Intradermic treatment with chaulmoogra oil, or esters.

Leprous reaction: Diet of fever patients. Emetic of potassium in small doses (20–40 mg. per day, intravenous, repeated ten to twenty times). Calcium.

Stenosis of the larynx: Calcium intravenously. Pulverizations of adrenaline. Tracheotomy if necessary.

PROPHYLAXIS

When once the contagion by direct contact, however limited, and the weak sterilizing power of therapeutics are recognized, isolation appears as the only real resource. This isolation must have in view especially, if not exclusively, the L. cases with numerous bacilli, that is, cases of open leprosy. It may happen, however, that N. lepers are infectious at certain moments. The chief concern is to protect healthy children and to separate them from their sick parents. Isolation must be voluntary: the leper is not guilty and is less dangerous than a tuberculous subject. Obligatory isolation leads to evasion and concealment of the sick.

Isolation may be:

1. *Individual,* the patient having his own house or at least room, his

table utensils, his linen, etc. Theoretically possible, this system is neither very practical, nor very agreeable in view of the difficulty of maintaining social relations. It has been efficacious in civilized countries with comprehensive patients.

2. *In closed establishments:* often separating the sexes. On a voluntary basis these establishments can exist and there are numerous examples in India, Egypt, Nigeria, U.S.A., etc. Their drawback is their great cost if we wish to assure the patients a sufficient standard of living. The establishment tries, however, to be self-supporting, thanks to various agricultural and industrial activities.

3. *In isolated agricultural villages:* a practical system in primitive and agricultural countries (Congo, Nigeria). In the Congo lepers live without separating the sexes, in villages of native type and as self-supporting as possible. Isolation is evidently less perfect but the system is cheap and assures the patient an almost normal lot. Medical treatment must be given. Infant asylums must be provided for the isolation of healthy children. The application assumes a fairly strong endemic. Otherwise the lepers must be grouped in places distant from their native villages and the isolation resembles then the one cited in (2) above. Three to four hundred lepers to a village appear to be a good average. Arable lands must be at their disposal. Hospices or hospitals annexed to the village must be provided for the incurables and for cases of intercurrent illness.

Education: This aims at spreading correct ideas of the disease, neither carelessness nor exaggerated fears; ideas concerning infection, probable manner of transmission, special susceptibility of children, advice for isolation and treatment, precautionary measures, etc.

Itinerant treatment is sufficient for light cases. It is part of the education and ensures a knowledge of all cases. It is both general and specific.

Census: In the Congo, a census is made systematically in certain areas with classification of the entire population. Doubtful cases are reviewed every six months, light cases are given itinerant treatment, serious cases are isolated. When there is no methodical census, the opening of dermatologic clinics brings forth the cases.

Patients who show no clinical or bacteriologic signs during two consecutive years are paroled and re-examined every six months for three more years.

2. MYCOSES

We shall adopt an anatomo-clinical classification, but for all dermatoses not specifically tropical we refer the reader to dermatologic treatises.

The clinical diagnosis of epidermomycoses (tinea, eczema marginatum-erythrasma, circinated herpes, versicolor pityriasis) is usually easy, and would be assisted by classic examination with potash (see further) or with chlorallactophenol. The diagnosis of mycoses of the extremities of dysidrosic, eczematiform or keratosic aspect, may be clinically difficult. Microscopic examination is a necessity. The onychomycoses will also be diagnosed with the microscope.

Mycosic folliculites (Kerion, Sycosis) lead to confusion with microbial manifestations. Here again microscopic examination will be the deciding factor. As for deep dermic lesions, of nodular, verrucous or ulcerous character, these might resemble syphilids, pianids, tuberculosis, leishmaniasis, etc. Visceral lesions simulate tuberculosis and other infections.

All these factors must induce the practitioner in the warm climates to have recourse frequently to elementary mycologic examination. This can be done in fresh preparations without other contrivance (not too thick pus) but generally it is better to clear up with caustic potash (10–40 per cent), and slightly warmed between slide and coverslip (squama, hair, etc.) (see Appendix C).

With expectoration, besides fresh examination, a Gram and a Ziehl-Neelsen are also advisable.

Cultures and guinea pig inoculation can eventually be requested at the laboratory.

(A) EPIDERMIC MYCOSIS

(a) *Tinea capitis* (*Tonsurans*) Ring worm.

Infection of hair sheath peculiar to children and disappearing at puberty. The fungi in question are *Microsporon* or *Trichophyton,* the former *ectothrix,* the latter *endothrix;* they are cosmopolitan affections, fairly common in the tropics. According to Keyzer, in Indonesia, European children or half-castes only are attacked. The condition is characterized by alopecias in patches, with broken and split hair, epidermic desquamation, and a chronic nonsuppurative evolution. Examination of hairs, after clearing with a solution of caustic potash at 40 per cent, shows myceliums which fixes the diagnosis with other hair destroying dermatoses (alopecia, psoriasis, folliculitis, secondary syphillis, etc.).

Favus (*Tinea favosa*) caused by *Trichophyton* (*Achorion*) *schoenleini,* principally attacks the scalp, penetrates the epiderm more deeply, terminating with scars and permanent baldness. There is not the slightest tendency to spontaneous cure at puberty.

Diagnosis is based on the existence of epidermic scabs of concave form (scutula), on the particular mousy smell which may be absent sometimes, and finally on microscopic examination.

(b) *Tinea glabrosa: Glabrous skin ring worm.* Circinated herpes ring worm.

The disease is caused by different *Trichophyton* and *Microsporon*, giving erythematosquamous and vesiculous lesions with marked tendency to radiary extension. Sometimes pruritus exists. Diagnosis must distinguish from psoriasis (more squamous), seborrheic dermatitis, syphilids, leprids, but is based on rapid radiary extension, the vesiculous aspect of edges and the discovery of the fungus.

Pytiriasis versicolor (tropical variety) *Tinea flava*

This affection deserves to be pointed out because of its extraordinary frequence in several tropical populations. In the Congo it is quasi general and known under various native names (loto, dioto, lobiki). Natives rarely ask for medical treatment, which is not easy in any case.

The affection is characterized by buff colored, squamose spots, often forming enormous patches, especially localized on the neck and intermammillary triangle, the torso, and face.

The intensity of infestation is more marked than in Europe. Apart from this, prognosis is quite mild and the clinically simple diagnosis may be confirmed with the microscope by the discovery (with caustic potash) of round elements associated with mycelium. (*Malassezia furfur*).

Tinea imbricata, Tokelau

This is specifically a tropical disease (mainly Far East and Pacific) caused by diverse *Trichophyton concentricum*. The marked squamous lesions often have a geometric concentric appearance. Extremely chronic evolution, often very extensive, giving a more or less ichthyotic aspect.

Prognosis is very serious, given the resistance to treatment. Generally, diagnosis is clinically easy because of the concentric aspect of lesions.

Treatment, which is difficult, utilizes the various fungicides: chrysarobine, sulphur and salicylic acid, benzoic and salicylic acids.

Tinea cruris

Marginal eczema of Hebra, dhobie itch*, athlete's foot, Hong Kong foot, etc.

Affection principally caused by *Epidermophyton floccosum* and more frequently observed in the tropics.

Lesions differ only slightly from those of circinated herpes but attack particularly the genito-crural region or sometimes the armpits. Pruritis is variable. Extension, clear margination helps the diagnosis, which is determined by laboratory examination.

Treatment: If the case is acute, and extremely erythematous: local bathing with permanganate at 1/4,000 followed by gentian violet at 1 per cent in 20 per cent alcohol, followed up by antiseptic powders (salicylated talc, oxide of zinc). Milder cases would be treated with iodated alcohol at 1 per cent, or tincture of Castellani (fuchsine 1 per cent in phenicated water) at 2 per cent, resorcinated at 5 per cent or Whitfield's pommade: salicylic acid at 6 per cent and benzoic acid at 12 per cent, followed by antiseptic powdering: proportionate salicylated talc or talc with calcium proportionate at 15 per cent, etc.: sterilization of clothes.

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* Itch of the dhobies, washermen (India).

On the foot, less frequently on the hands, the affection is particularly tenacious and of varied clinical type: squamous and hyperkeratosic type (dry region of foot), intertriginous type of interdigital spaces with moist scabs and red depth; vesiculous type also found on dry parts of feet.

The affection is to be distinguished from simple hyperidrosis, dysidrosis, and nonparasitic keratosis. It can be caused by the simple fungi of thrush, *Candida (Molinia) albicans.*

Prognosis is locally serious. A cure demands careful treatment and disinfection of shoes and everything in contact with the feet.

Treatment should be as given above. Keratolytics (salicylicated acid ointment) are used in dry cases, and compresses of permanganate solution in erythematous cases.

Trichophytosis of the nails: Extremely resistant form, characterized by brittle, thickened nails with epidermic debris where the fungus can be found.

Trychophytids and epidermophytids: By this is meant reactions of sensitivity to allergens emanating from some focus of mycelian infection. The aspect is that of a cutaneous reaction, eczematiform or dysidrosiform. The diagnosis may be aided by verification of the primitive focus and a positive skin test to Trichophytine.

Thrush: Affection more frequently superficial, sometimes determining epidermomycosis but attacking especially the mucous tissues and caused by *Candida (Monilia) albicans.* Visceral localizations exist. The parasite is quite cosmopolitan.

(B) DERMO-EPIDERMIC MYCOSIS

Kerion of Celsius, trichophytic sycosis (Folliculitis).

The reaction opposed to the parasites in question, especially *Trichophyton exothrix* of animal origin, is more violent, attacks the derm and suppurates. Kerion forms inflammatory medallions, especially on the scalp, sycosis attacks the entire beard with fairly deep folliculitis.

The differential diagnosis, aided by parasite research, should, for the beard, be made from staphylococcic sycosis with folliculitis (the latter more acute and usually more superficial).

With the Negro, one observes fairly often pseudo-acne of the beard which is due to the fact that curly hair has a tendency to "ingrow," producing an irritation. In these latter cases, a complete shave would be the remedy.

Trichophytic sycosis does not appear to be common in Central Africa where, in fact, horses are rather rare.

Chromoblastomycosis, Dermatitis verrucosa

Affection caused by *Hormodendron*, observed in different tropical and nontropical countries.

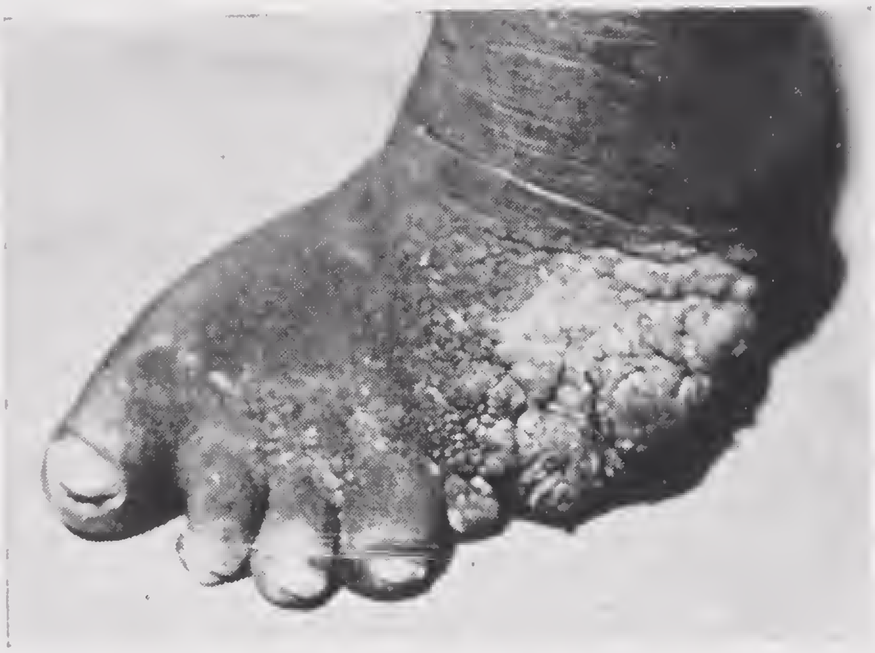

FIG. 58. MOSSY FOOT-LIKE CONDITION, CONGO (Coll. Tropical Institute, Antwerp)

Lesions situated on exposed parts and generally unilateral resemble ring-worm in the beginning, but become nodular and verrucose. A certain number of nodules may ulcerate.

Evolution is very chronic (several years) and is accompanied with deep fibrosis with elephantoid state. General health is little affected, if at all.

Diagnosis will be aided by microscopic examination or biopsy, which will show brown elements, more or less round and dividing themselves by splitting. Treatment is difficult: iodide, iodine, etc.

Mossy foot

Under this name, there has been described in several tropical countries (America, Africa) a verrucose dermitis of the foot which does not seem of mycelian origin. We are inclined to agree with Loewenthal who considers it as a continuation of elephantiasis. Facts observed in the Congo appear to us to agree with observations made by this author in Uganda.

Rhinosporidiosis, Rhinosporidium seeberi

Definition: Infection of the mucous membrane, more rarely of the skin, of polypoid character, caused by an organism, *incertae sedis.*

Geographic Distribution: mainly tropical (India, Ceylon, South America, etc.).

Etiology: The disease exists in domestic animals. The parasite takes a spheric form of 6–7 μ, becoming a kind of cyst of 100 μ which one compares to a sporangium containing numbers of small spores (16,000). The sporangium reaches 200 to 300 μ, then bursts and liberates the spores.

Pathology: The appearance of these sporangia in the midst of an ordinary inflammation with lympho- and plasmocytes is quite characteristic.

Symptomatology: The polypoid aspect of lesions on the nose, on the skin (specially facial), pharynx, larynx, and eyes make one consider Rhinosporidiosis.

The *diagnosis* should be made with certain syphilitic condylomes, or with common nasal polypes. The microscope or, better, histologic examination will be decisive.

Prognosis: Relatively mild given the absence of visceral lesions. Laryngeal obstruction is possible.

Treatment is surgical. Pentavalent antimony in addition has also been advised.

Maduromycosis, Mycetoma, Madura Foot

Definition: Chronic affection nearly always localized in the foot, caused by different genera and species of fungi, characterized by a chronic inflammatory swelling with fistulation and elimination in the pus of different colored "grains," white, yellow, red, black, of mycelian structure.

Geographic Distribution: The term Madura foot alludes to the discovery of the disease in southern India (Van Dycke Carter). Actually it has been observed nearly everywhere in the tropics but less frequently in temperate countries of Europe and the Americas.

Etiology: Walking barefoot causes small wounds which are a source of infections by ground saprophytes, etc. Isolated germs are widely varying: (1) *Nocardia* or aerobic *Actinomyces** (a dozen species) belonging to the Schizomycetes. (2) *Madurella, Indiella*, etc., belonging to Fungi imperfecti (about 15 species). (3) *Allescheria, Aspergillus, Sterigmatocystis, Penicillium,* belonging to the *Ascomycetes* (4 species).

The color of the grains may not be sufficient to identify the nature of the fungus. Grains are 0.5 and 2 mm. in diameter, of irregular form, and after clarifying by potash show a mycelian structure, variable according to the class of parasites. Culture may be made in a Sabouraud medium but inoculation of animals fails. Paramycetomes exist where the fungus does not form grains.

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* *Actinomyces bovis* (anaerobic) is the agent of Actinomycosis, the pathology of which is very close. The organism is probably a buccal saprophyte. Further clinical Actinomycosis may be caused by other *Nocardia.*

Pathology: It is a chronic inflammation of conjunctive and bone tissues with a mixture of suppuration and fibrosis, and where the presence of grains or filaments (paramycetomes) would supply the etiologic element.

Symptomatology: The disease begins by one or two firm infiltrations appearing on the foot. Usually, when the patient consults, the foot is tumified, showing superficial nodules of which some are fistulized giving issue to slight and granular pus. The foot becomes larger and larger, the plantar surface is convex with the toes not touching the ground. The back of the foot is full of fistulas while probing shows decayed bone. The leg is atrophied. There is little or no pain and little or no general signs nor metastasis except in the case of microbic complications.

Prognosis: Functional prognosis is unpropitious, the extremity being condemned. Vital prognosis is good, although finally, often after years, cachexia may appear (additional infections).

Diagnosis: The localization and aspect are characteristic. Precise diagnosis is given by examining pus with lens, then clarifying the grains with caustic potash at 30 per cent and microscopic verification of their mycelian structure.

The diagnosis of the fungus species involved requires a specialist. X-rays can specify the bone condition.

Treatment: Amputation is the only effective resource. Iodide is usually inactive. Sulfonamides or penicillin can be tried and may limit additional infection.

Prophylaxis: It is essential to wear shoes. Small cuts or wounds on the foot must be disinfected.

(C) DEEPLY LOCATED MYCOSES, EVENTUALLY VISCERAL*

North American Blastomycosis: This cutaneous-visceral form is observed in the U.S.A. with agricultural workers and is probably of animal origin. It is caused by a fungus, *Blastomyces dermatidis.* There exist primary and secondary lesions, by propagation in the skin, papulo-verrucous or papulo-ulcerous. Lesions leave scars. The general health is little affected, if at all.

Diagnosis will be rendered possible by the discovery of fungus cells, often rare, of oval or spheric form with thick walls, and able to bud out. In culture, filaments appear and therefore the organism is not a real fungus. Mice are receptive.

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* We omit Actinomycosis and Sporotrichosis, usually treated with cosmopolitan diseases.

Visceral or bone localizations produce a variable symptomatology with serious general fever phenomena and a grave prognosis.

Diagnosis of the pulmonary form, most frequent, is related to tuberculosis (even histologically) and is determined by the absence of bacilli and the presence of *Blastomyces* cells, which never produce endospores.

Treatment utilizes iodium and iodides associated to vaccino-therapy of desensitization.

European Blastomycosis or *Cryptococcosis:* Caused by *Cryptoccocus neoformans,* it is an affection known in Europe, America, and Oceania. Lesions are cutaneous (nodulo-ulcerous), pulmonary, and with a marked cerebro-meningeal frequency. In the latter case, the clinical aspect is most frequently meningeal with subacute evolution, or chronic nonfeverish, but with fatal prognosis.

Inflammatory reaction is much less marked than in the American form in spite of abundant fungus cells having a thick coating and often budding. One may find these cells in the cerebrospinal fluid which is often modified. Mice are receptive.

Treatment is based on sulfonamides and perhaps penicillin (this by cerebrospinal injection in case of meningitis).

South American blastomycosis: This is due to *Paracoccidiodes* (*Blastomyces*) *brasiliensis:* The primary lesion is more often buccal and papulo-ulcerous. The skin and the lymph glands are infested, and one may observe diverse visceral lesions also. The fungus cells have a double contour and budding in multiple manner which is characteristic with them.

Cultures on Sabouraud medium also produce mycelium. They are pathogenic for guinea pigs and mice.

Prognosis is very serious and treatment is conducted as for North American blastomycosis, i.e., desensitization and iodide.

(D) COCCIDIOIDOMYCOSIS

Definition: Chronic infection caused by a fungus named *Coccidioides immitis* with localization frequently pulmonary. This affection has been known for only a short time and is still insufficiently investigated.

History and Distribution: This disease was described in 1892 in the Chaco (Argentine-Bolivian border) but has appeared as an important affection only quite recently, especially in central California, during the training of American air force personnel.

The dry and warm regions of southwestern United States are the principal focus.

Etiology: The fungus appears in the tissues in the form of small spheres producing endospores which produce spheres themselves. In culture, one observes segmented hyphae with subsequent chlamydospores. These are easily infectious for experimenters.

Transmission is effected by inhalation of dust containing spores. It is not certain that the patient is contagious, nevertheless, pathologic exudates are transmissible to animals. With man, there have been infections through skin excoriations.

It is possible that rodents play the role of virus reservoirs.

Pathology: This concerns a granulomatous infection which evolves like tuberculosis (caseification, cavernification, calcification). Cold abscesses, meningites, exudative pleurisies have been observed. Dissemination by the blood is possible.

Symptomatology: (a) Paucisymptomatic or asymptomatic form recognized by the appearance of a positive skin test. There may be a certain degree of fever, of respiratory catarrh, and sometimes of nodose or polymorphous erythema which would exist in 5 per cent of the cases and subsequently leave immunity. This form is the most frequent. Prognosis is generally favorable.

(b) Pulmonary form with functional symptoms, stethacoustic or radiologic, imitating diverse tuberculous manifestations but of relatively mild type, and fairly easy to cure. Prognosis remains favorable in spite of the alarming aspect under x-rays.

(c) Generalized form, rare but serious. This, however, is the most frequent form in colored races. Diverse localizations, cold abscesses, meningites associated with acute or chronic infections conclude fatally.

Diagnosis: This is clinically difficult. Newly declared cases may simulate influenza and the bronchopathies, pulmonary and metastatic cases. The disease is reminiscent of tuberculosis, but this latter will be eliminated by bacillus research. On the other hand the coccidioidomycosis gives: (1) Positive skin test by means of an extract of culture in liquid medium (0.1 cc. of the coccidioidin at 1 per cent is injected in the derma). Reading after forty-eight hours. This test evidently indicates a present or past infection. The frequency of nonspecific reactions has not been determined yet. (2) Precipitation or fixation of the complement in presence of mycosic antigen and serum from the patient. This reaction corresponds to active infections. (3) Microscopic research of spherula in the expectoration (not easy). (4) Inoculation in animals (mice, guinea pigs) of cultures or pathologic products. (5) Blood sedimentation has only prognostic value. X-rays cannot provide a reliable etiologic diagnosis, given the possible confusion with tuberculosis, atypical pneumonias, etc. The relative mildness of evolution in opposition to the clearness of radiologic signs may be significant. Prognosis is favorable except in generalized forms.

Treatment is purely general and symptomatic.

(E) HISTOPLASMOSIS

Definition: General affection caused by *Histoplasma capsulatum* resembling strongly kala-azar by its evolution.

Geographic Distribution: Fairly cosmopolitan, the disease is chiefly known in warm countries (America, Java, South Africa).

Etiology: H. Capsulatum appears in the tissue as a intracellular parasite of fairly small dimensions (1 to 5 μ), sometimes with buds and filling the cells. Culture is chiefly of the yeast type with associated mycelian aspect (Sabouraud's medium) and shows itself pathogenous (guinea pig, mice). Distribution in primitive nature is not specified and entrance in the system would be either digestive (infancy) or pharyngeal (adult).

Symptomatology: In children, one notes a subacute entiritis with general disturbance, hepato-splenomegaly, anemia, leukopenia, and fatal evolution after a few weeks. Adults present a more chronic evolution with analogous symptoms but also frequently there are bucco-pharyngeal ulcerations, and cervical adenopathy. Isolated, the latter may simulate Hodgkin's disease. Commonly observed are pulmonary lesions, even primitive, simulating tuberculosis. Endocarditis has also been met with.

Prognosis is fatal.

Diagnosis is far from simple: kala-azar, aleukemic leukosis, mucocutaneous leishmaniasis, syphilis, etc., may be considered.

The parasite must be looked for in the reticulo-endothelial blood cells, in the spleen and bone marrow.

Culture shows considerable thick coated chlamydospores with protuberances.

Treatment: Antimonial compounds are advised.

3. YAWS*

Definition: Contagious affection caused by treponema closely related to that of syphilis (*Tr. pertenue,* Castellani 1905). Yaws differ from this latter disease by its nonvenereal mode of contagion and its primary extragenital lesion, by its localization almost entirely cutaneous, and its nontransmission through the placenta. From a parasitologic, historic, serologic, and therapeutic point of view, however, the identity is complete. It is not surprising that certain pathologists hesitate at considering yaws as a "good species."

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* Synonym, Framboesia tropica; French, Pian.

HISTORY

Yaws was described by Oviedo in the sixteenth century (Antilles) and by Bontious (Insulinde in 1629) under the name of "Amboine" smallpox. Sydenham maintains the unicist theory that European syphilis of the sixteenth century is of yaws origin: trading of yaws-infected Negroes, with subsequent infection of America and Europe. It appears to us that the lapse of time between the discovery of America and the syphilitic wave over Europe is really too short to justify Sydenham's theory. In 1905, Castellani described the spirochete observed in the disease called "parangi" (yaws) in Ceylon.

GEOGRAPHIC DISTRIBUTION

Trans-Saharan Africa is the principal and possibly primitive focus. Indo-China, Indonesia, Melanesia, Polynesia, Ceylon, and tropical America are also strongly affected. The Indian peninsula is little affected except in the Indo-Burmese region. Europe appears to be totally spared as well as the Mediterranean basin. Nevertheless, the diseases formerly described under the name of Irish pimply scurvy and of extragenital syphilis of Ruthenia, etc., may make one consider yaws. It is more a matter of nonvenereal syphilis and such is doubtless the case of Mesopotamian Bejel (see further). During the slave dealing epoch, yaws would have existed in the U.S.A. (North Carolina) where, furthermore, one sees cases here and there imported from tropical America.

ETIOLOGY

Treponema pertenue is morphologically identical with *T. pallidum*, discovered previously in the same year by Schaudin.

T. pertenue is found in yaws granules in the epidermis, in lymphatic glands, the spleen, and the bone marrow. It must also exist in the blood, since the latter is infectant, but it has not yet been discovered here. Like *T. pallidum*, the organism has not been cultivated. Experimentally, the monkey and the rabbit are sensitive.

TRANSMISSION

Yaws is transmitted to man by direct contamination of cutanous erosions or by indirect contamination due to flies or other insects. Auto-inoculation from an initial lesion is possible. Kumm, in 1935 at Jamaica, incriminated a small fly, *Hippelates pallipes*, which would transmit by regurgitation. *T. pertenue* also rapidly traverses flies' intestines and is virulent in their excreta. Mechanical transmission by *Aedes aegyti* has been suspected in South America.

Immunity: Yaws appears as an infantile disease and because of this fact adults are often immune or, what is more likely, semi-immune or in a state of premunition. Experimentally, with man as with animals, an actual immunity slowly develops against new inoculations, even heterologic and possibly even against syphilis. Cases of reinfection after treatment, such as are described in syphilography, are unknown to us. Here as elsewhere it is probable that chemotherapy is unfavorable to immunization, that is, if effective, which is probably rarely the case given the brevity of treatment.

Syphilis and yaws: The absence of cross immunity demonstrates the antigenic difference between two germs, but not necessarily a specific difference (zoologic or botanic). The example of the "serum-fast" trypanosomes, of the recurrent spirochetes of various attacks, and of bacterial variants should induce prudence.

In animals, the immunity created by an initial attack of yaws is sometimes incomplete, and sometimes complete toward syphilis. Syphilis would give complete immunity to yaws, which would be less virulent or eventually devoid of a partial antigen.

In man, Jahnel and Lange, and van der Schaar were unable to inoculate general paralytics with yaws. The former experience of Charlouis (inoculation of syphilis in a yaws subject) can possibly be explained by a primary period of infection insufficient to obtain immunity. Recently, however, Findlay and Wellcox have infected with syphilis a tertiary degree yaws case, affected for 12 years and treated with 914 (3.6 Gm. in all). Epidermiologic observations made in countries where yaws exists are contradictory: according to certain observers, yaws has served as protection against syphilis in certain Pacific islands. In the Congo, syphilis appears to spread little in Mayumbe, where yaws is prevalent, and yet spreads very easily in Nepoko, where yaws is just as current.

In experiments with animals, histology shows certain differences between the two affections which are difficult to interpret. Parasites of yaws install themselves especially on the epidermis, those of syphilis on the mesodermis.

To conclude, both parasites are undoubtedly closely related, with only faint differences in experimental pathology. Yet, clinically, we have two distinct entities, and there is nothing which allows us to suppose that one may be transformed into the other. The Congo natives, good observers, make a clear distinction. To us it seems logical to take facts at their true value and not according to a phylogenic point of view.

PATHOLOGY

The primary lesion shows important alterations of the two superficial layers of the skin. There is edema of the epidermis, hypertrophy of the interpapillary crests, a polymorphonuclear infiltration, hyperkeratosis, depigmentation. The central zone of the lesion is deprived of epidermis. The derma and even the superficial layers of the hypoderma are infiltrated with plasmocytes and lymphocytes. The spirochetes are found in the epidermis and the superficial parts of the derma.

The developed secondary lesion is remarkably papillomatous. The epidermis, still present, shows acanthosis, hyperkeratosis with scabs, microabscesses, and spongiosis. The papillary derma is infiltrated with plasmocytes and lymphocytes but the deep layers are little inflamed. As in the primary lesion, the parasites are found superficially (epidermis and superficial derma).

The late tertian and quaternary lesions are very syphiloid. The vascular alterations are generally not well marked in yaws.

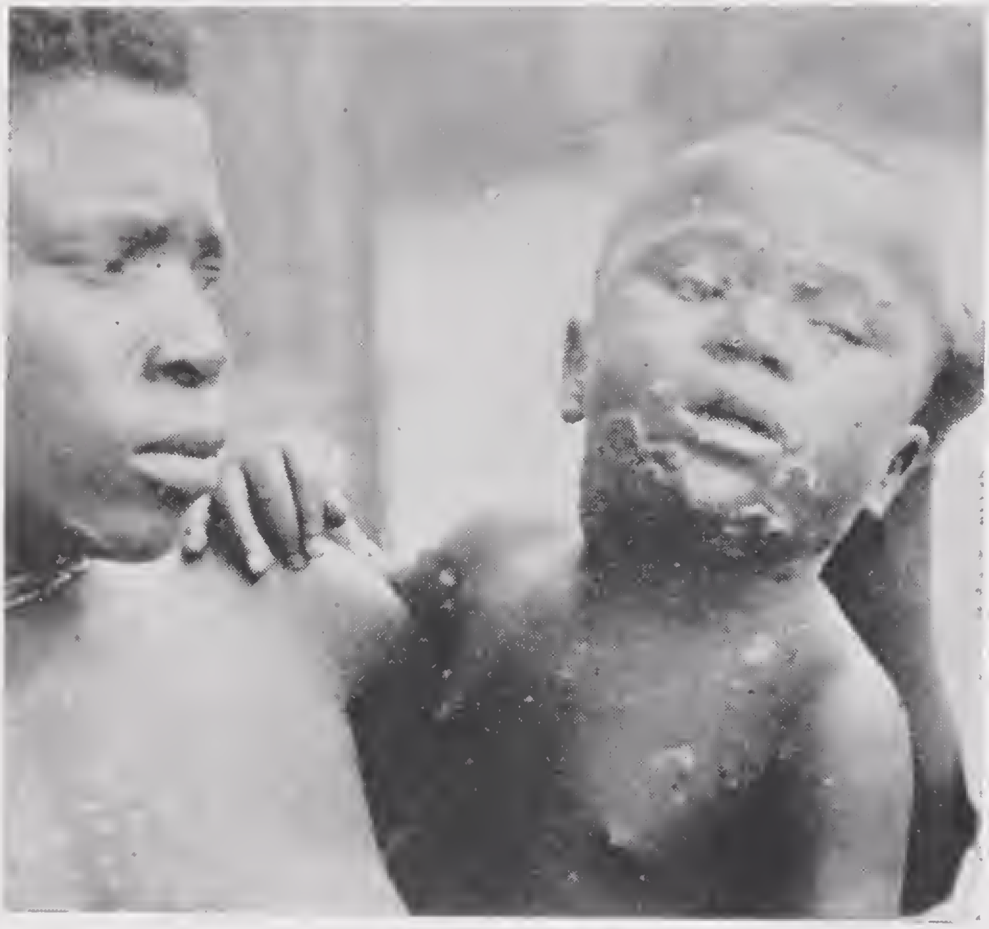

FIG. 59. SECONDARY YAWS
Circinated, papulosquamous lesions, Congo (coll. Tropical Institute, Antwerp)

SYMPTOMATOLOGY

Incubation: This would be from two to four weeks (Paulet's inoculation). Evolution then follows a systematization which clinically as much as serologically follows syphilis. There may also be some vague general prodromes.

Primary lesion. According to different authors (Montel, Keyzer, Williams) this takes the aspect of a papulo-ulcerous lesion, with a nonindurated base, eventually becoming pimpled and of lengthy duration.

The localization is extragenital, i.e., the extremities, face, etc. This primary lesion may finally spread, while becoming raspberry shaped, and completely simulates an extensive secondary lesion. This is, then, the "mama-yaws" of different tribes. A certain number of writers consider that the primary lesion is, from the start, the secondary raspberry form type. But this supposition is doubtless inaccurate.* The primary lesion may be accompanied with adenopathy. As a matter of fact the description of primary yaws still demands a greater degree of precision.

Second incubation: It lasts from one to three months, and is followed by generalization, above all cutaneous, but also with infectious phenomena including nocturnal headache.

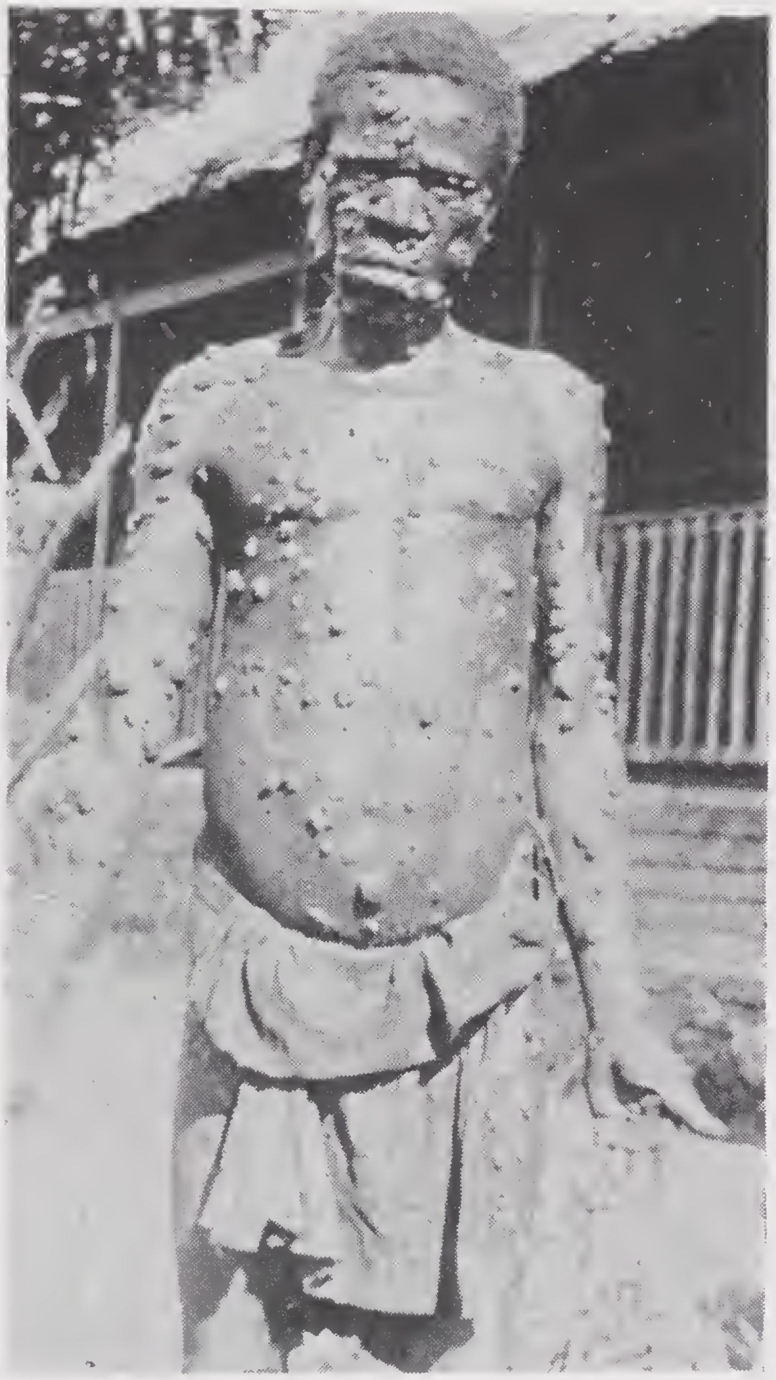

FIG. 60. SECONDARY YAWS
Typical framboesia tropica from the Congo (coll. Tropical Institute, Antwerp)

Secondary period: The secondary eruption, with which the terminating primary lesion is often still contemporary, may assume various aspects, including, exceptionally, an authentic roseola (Montel). (1) Rather small macules with parakeratosis and desquamation. (2) Groups of small papules may follow these macules. (3) Isolated papules, with small scabs which, when picked off, show a rather raspberry shaped appearance. These small papulae develop and end by becoming the real yaws raspberry, yellowish element from a few mm. to 1 cm. in diameter and even more. When the scab is taken off, under a thin layer of pus is revealed a nodulous pink epidermoid surface (mucous body of Malpighi).

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* Certain experimental inoculations have developed into secondary type lesions but we may wonder if they were with absolutely sterile subjects, this being difficult to discover in certain countries.

These elements may appear over the whole body, but their favorite sites are around the orifices, where they develop extensively. The mucous tissues are spared or, at the most, little touched by a neighboring cutaneous element. At the anus or the genital region the scab disappears and resemblance with syphilitic flat condyloma is very marked. During the course of later evolution, one observes elements of analogous structure but drier and circinated or hemicircinated.

In spite of, here and there, symptoms of precocious tertiarism with ulceration, these secondary elements have the character of syphilids of the same period, i.e., multiplicity, resolutive characteristics.

A pigmented spot may exist for some time, but very rarely does a scar show slight suppuration farther than the epidermis. On the foot, infrequently on the hand, secondary elements, often tardive, break through the corneous epidermis. This is the "crab yaws" with vague papillomatous aspect, painful fissures of the corneous strata. Palmo-plantary lesions, often circinated, papulo-squamose, or slightly raised, are frequently seen.

Secondary yaws spares mucous tissues, viscera, and the nervous system. A certain degree of adenopathy is sometimes observed (epitrochlean lymph node). Secondary evolution is lengthy, several years generally, with various and delayed recurrence.

Tertiary yaws: Like tertiary syphilis, it has two important characteristics: a tendency to localization, and an ulcerous character which indicates the organism's immunization and allergization. The absolutely syphiloid appearance is such that only the history of the patient and his family can give precise diagnosis.

The following signs may be noted:

1. On the skin: (a) Tertiary tuberculo-ulcerous yaws in patches often like ring worm, and the affection decribed in the Congo under the name of nodular and ulcerous dermatosis must be placed in this category. The resulting scars may become very ugly or ankylosed patches. (b) Raw or ulcerous yaw gums leave, in this case, an ulcer with sharp edges of syphilitic type.

2. In deep conjunctive tissues: (a) juxta-articular nodosities (see further). (b) Periostitis with thickening and bone deformation, dactylitis, sword edged tibia. One relates yaws with goundou, and hypertrophic

osteitis of the superior maxillary. We give a separate description of this condition (see further).

3. Ulcerated muco-cutaneous lesion called "gangosa" affecting the center of the face (see further).

Delayed or "quartan" secondary lesions: These are nonulcerous, tenacious yet resolutive and, therefore, nontertiary.

One must cite, above all, punctuated or fissural palmo-plantar keratoses, often with spotted dyschromia on the back of hands or feet. Natives generally provide a very clear picture of the above and it is a fact that these symptoms constitute a fairly typical symptomatic complex. Submission to treatment is variable, dyschromia being stable. As this is often observed in old subjects, perhaps one should impute the condition to senile modification of the skin (action of light?).

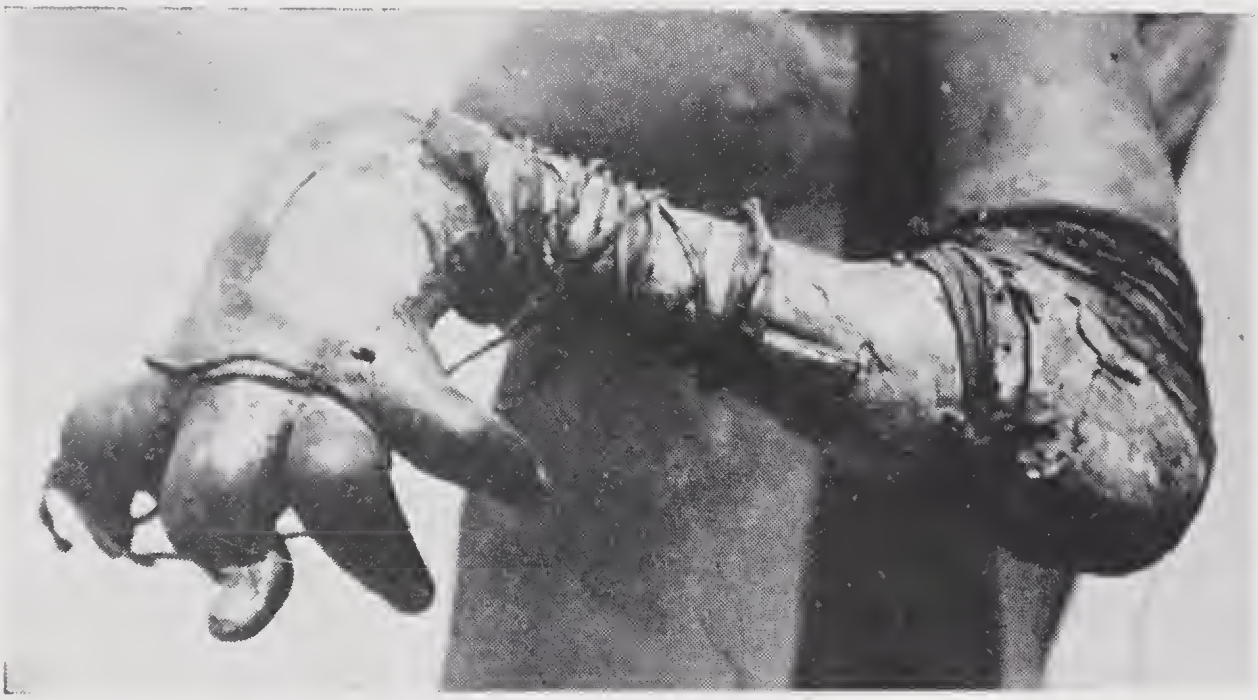

FIG. 61. TERTIARY YAWS
Dactylitis, arthritis, and ankylosis (coll. Tropical Institute, Antwerp)

Furthermore, we have also noted small unusual dyschromic patches and tenacious circinated papulous lesions. In both these cases one might consider leprosy, but a proof treatment decides the diagnosis.

It is perhaps in this period that most frequently are noted arthralgias and, less frequently, exudative arthritis, that the Congo natives willingly attribute to yaws. All this needs unravelling from the mass of "chronic rheumatisms." Unfortunately the condition is often found in elderly subjects to whom arsenic and bismuth are sometimes offensive.

Visceral and nervous lesions: Most authors do not believe in their existence and nothing draws special attention in countries where yaws is prevalent, as is also syphilis most of the time. Cerebrospinal fluid is normal in yaws.

DIAGNOSIS

Primary yaws is rarely diagnosed. The ulceration is doubtlessly considered quite ordinary, and perhaps the native takes no notice of it.

Secondary lesions are easily diagnosed in typical cases. Multiplicity, yellow scabs, very mamilliformed, absence of mucous lesions and history of the disease. Rare elements, either of circinated type, or in damp parts of condylomatous type, are strongly syphiloid. Clinical diagnosis of the tertiary period is often quasi impossible between yaws and syphilis. The patient's history, absence of miscarriages may elucidate the case. Serologic reactions are those of syphilis; about 100 per cent positive in full secondary period, falling to 50 per cent in tardy cases. Spirochetal research does not distinguish syphilis from yaws and histology is also of little use here.

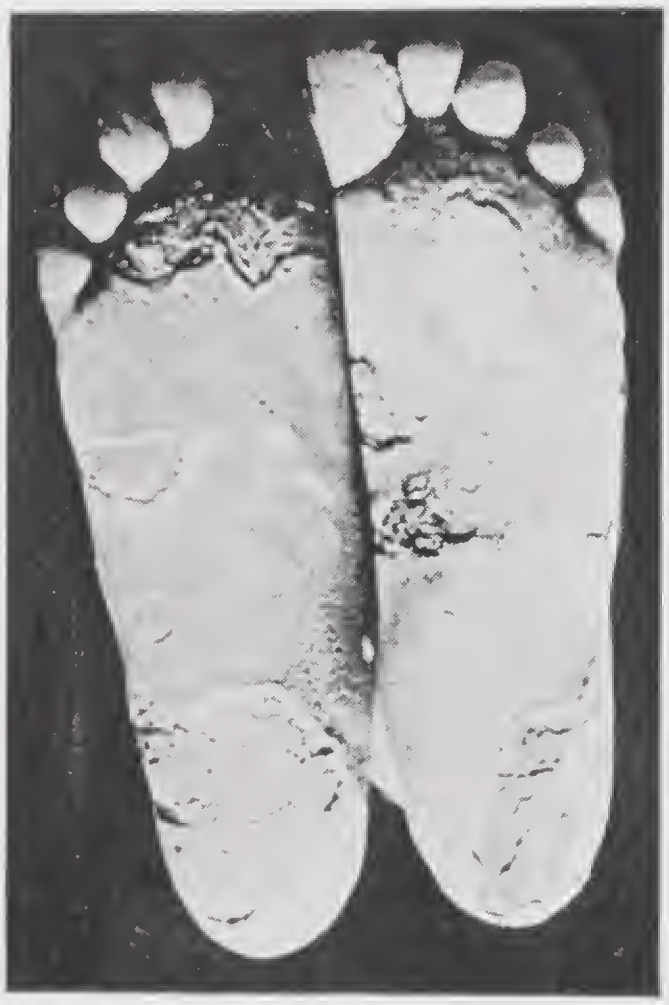

FIG. 62. YAWS
Late lesions on the soles, Congo (coll. Tropical Institute, Antwerp)

PROGNOSIS

This is favorable except in cases of tertiary lesion and less so of gangosa, the functional prognosis of which is grave. If yaws would decidedly immunize against syphilis, it might be considered to have its beneficial aspects, but this has not been established for all cases.

TREATMENT

Treatment is the same as for syphilis, but given the mildness, a minimum treatment is often applied, i.e., ordinary arseno-bismuthics for a period of two years.

American military authorities prescribe:

Four weeks bismuth + arsenic (neoarsphenamine or mapharsene).

Four weeks arsenic alone.

Eight weeks bismuth only.

Ordinarily we make 3 to 4 series of arseno-bismuthics with a rest interval of two months between each series. Neither this nor the preceding treatment guarantees the absence of relapse and the negativation of serous reactions.

Gold and antimony have a certain specific action, potassium iodide, salts of mercury also (this last metal is very badly tolerated by Congo natives). Penicillin is as equally active as in syphilis.

PROPHYLAXIS

The disease is more rural than urban. Prophylaxis consists in isolating the patients, and in rapid treatment (favorable action of dispensaries). Sores and ulcers must be protected with dressings. General hygiene, that of body and clothes, is essential, the proof being that Europeans very rarely contract the disease.

Bejel

Under this name, Mesopotamian Bedouins isolate a disease which is probably an irregular syphilis. It is contracted by ordinary contact in childhood and has a chronic evolution resembling yaws or syphilis. Primary lesions are rather badly specified, and in any case do not resemble syphilitic chancres.

Secondary lesions are of papulo-squamous type, often circinated. They are resolutive and without general symptoms. Tardy lesions are of gumma type, including affections of the skeleton and face, or else of more chronic type, nonulcerous, plantar hyperkeratose, juxta articular nodosities, periostitis. Serology and therapeutics are those of yaws and syphilis.

Juxta-articular Nodosities

Juxta-articular nodosities are subcutaneous nodules, apparently related with syphilis, yaws, or bejel. They are especially encountered on the posterior surface of the elbows, the back of the knees, and on the trochanters. They are generally few in number (for instance, only one to every articulation). They have a strong tendency to develop symmetrically. These very hard nodules frequently adhere to the skin but not often to the deeper tissues. Their evolution is indefinite. They do not ulcerate or greatly inconvenience. The natives very rarely consult on this ailment. The pathogenesis is not clear. Do they constitute chronic bursites? The histology sometimes shows a chronic granulomatous structure with giant and epitheloid cells and slight necrosis, more often a dense conjunctive tissue, very little vascularized. Spirochetes have been encountered, but only seldom. Although rather tropical, the disease has been met with in Russia, the U.S.A., etc., among people who had not been out of the country. This diagnosis is especially to be made with the nodules of *O. volvulus* (these are a little less hard) and confirmed by puncture or excision (absence of microfilariae or of filariae). The puncture of a nodule generally produces little exudation.*

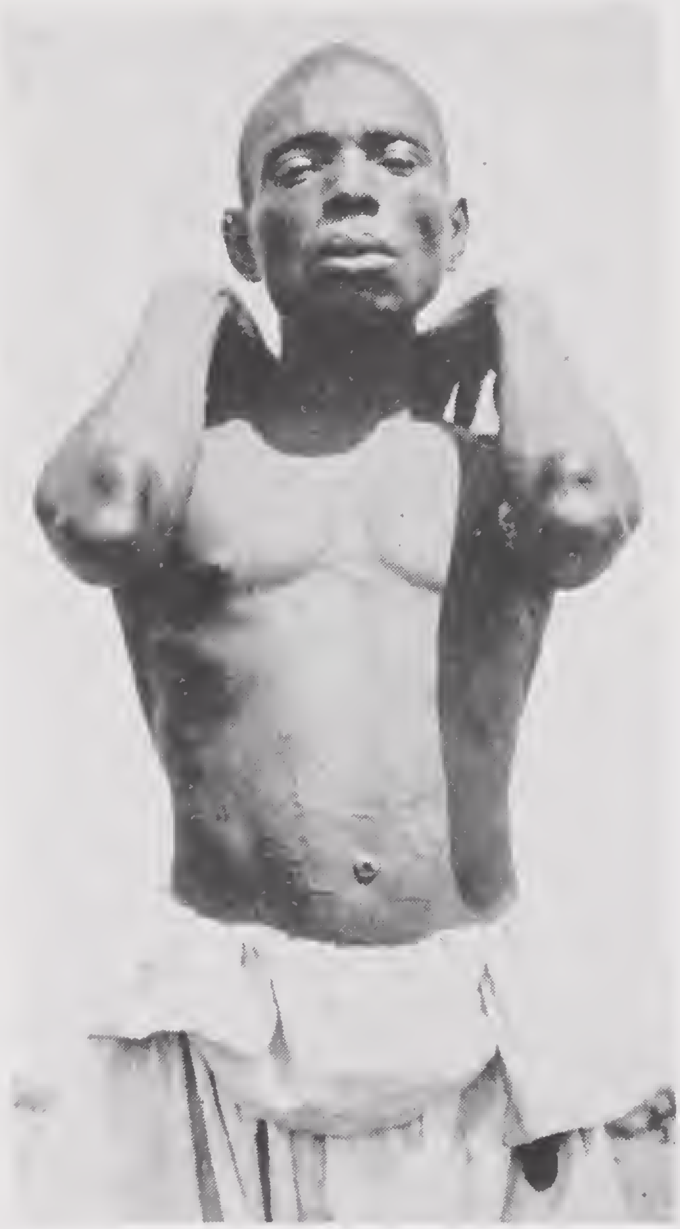

FIG. 63. JUXTA-ARTICULAR NODULES
Not related with Onchocerca infection (L. van den Berghe)

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* In Madagascar nodosities of an unknown etiology have been described. They are composed of uric acid and cholesterol and are found only on the high plateaus, especially among the Hovas. Tuberculosis is often associated with the condition (Fontoynont and Girard, 1946).

The treatment, which is seldom requested, is surgical. There is little or no response to specific treatment. Nonsurgical treatment might be advisable for cases in the first stages.

Gangosa

The name Gangosa is of Spanish origin and refers to the change of voice. The disease seems to be some form of ulcerous tertiary yaws. The ulcerous process most frequently begins in the skin and spreads rapidly to the center of the face, attacking the lips, the nose, the bones of the nose and palate. Finally, the whole region becomes a very disfiguring and disfunctional crater. Syphilis has to be considered in the diagnosis (onset usually from the depth), leishmaniasis, mycoses. The epidemiologic conditions, the history of the subject and his family, together with the different microscopic and serologic examinations and, if necessary, the trial treatment will assist the diagnosis. The latter can certainly not produce any satisfactory results unless it is applied in the early stages.

Goundou

This, too, is a clinical manifestation apparently connected with yaws. It is especially observed, but never frequently, in countries where yaws is prevalent (Tropical Africa, South America). The disease consists in a chronic and generally bilateral hypertrophy of the upper jaw and the nasal bones. This may result in osteocopic pains and eye trouble. The diagnosis must be made with tumors (osteomes) or metabolic bone alterations (Paget's disease). Specific treatment should be tried and, if necessary, surgical intervention.

4. PINTA*

Definition: Disease characterized by macules, sometimes depigmented, sometimes of a violet or slate blue color. The clinical description of the disease is still rather confused. The etiology, first ascribed to fungi, is actually related to a Treponema.

History: Vague descriptions of the "mal del pinto," or of pinta (in Spanish, "spot"), are found in ancient chronicles dating from the period of the conquistadores.

Geographic Distribution: The disease seems limited to central America, the West Indies, Colombia, and a few other South American countries.

Etiology: Herrejon, Fox (1927–1930) have suggested that the condition might be of a spirochetal nature. Numerous positive Bordet-Wassermann reactions and ultimately the finding of a spirochete in the lesions or the lymph nodes (Triena and Armenteros, 1938) have confirmed this theory. *Treponema carateum* (*herrejoni*), described by Brumpt in 1939, resembles *Tr. pallidum* and has not been cultivated. Inoculations to animals are still not well understood. Normal men are fully susceptible, syphilitics little, and patients who previously suffered from pinta are almost immune (Leon y Blanco). This disease of warm and humid countries affects almost exclusively Amerindians and colored races. It is rarely found in young children.

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* Synonyms: Carate (Colombia), Mal del pinto (Mexico), Azul (Chile), Boussarole (Haiti), etc.

The transmission is probably achieved directly by ordinary contact. Certain insects (flies, Cimex, Phlebotomes) are suspected.

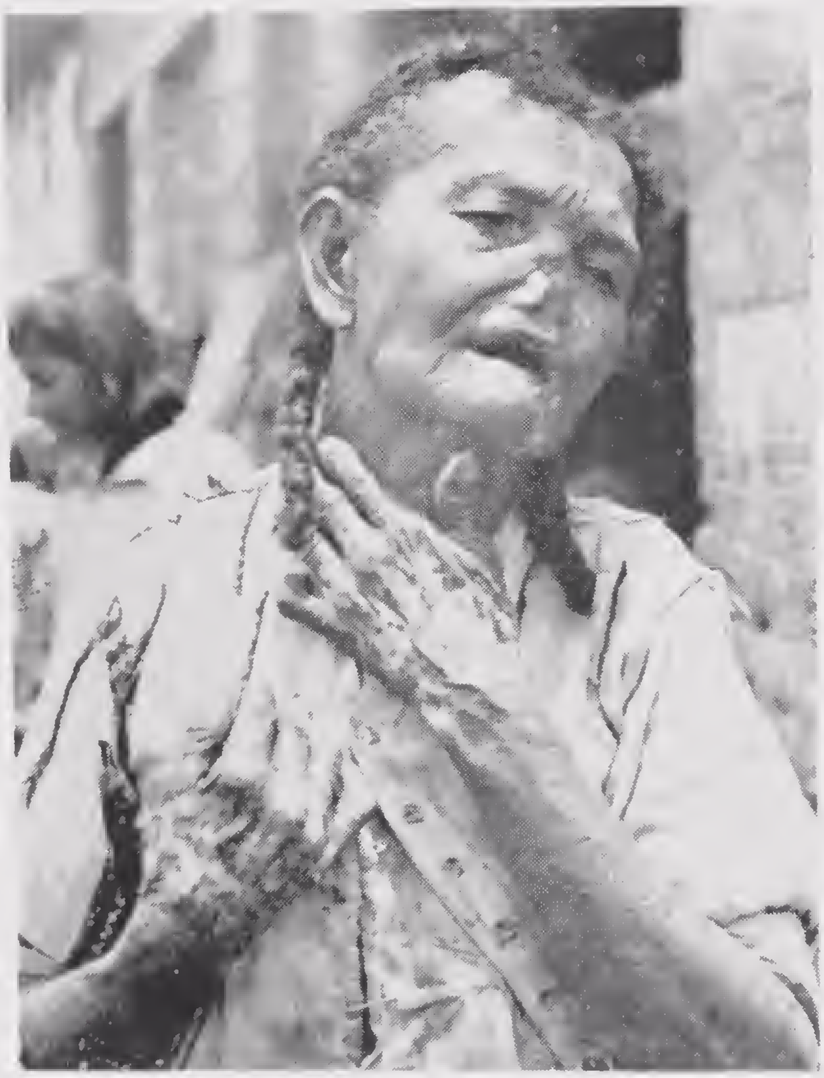

FIG. 64. GANGOSA AND PINTA
Case from Colombia (courtesy Dr. E. Brumpt)

Pathology: The typical lesion is a dermo-epidermic papule with hyperacanthosis and epidermic alteration, dermic infiltration with small cells extending more in depth than yaws, and an abnormal distribution of the pigment. The parasite is localized in the epiderm.

Symptomatology: Inoculation experiments indicate an incubation of seven to twenty days.

Primary lesion: A papule appears on an uncovered part of the body. This papule might extend considerably and reach an erythematous-squamous stage of slate blue tinge. It does not become ulcerated.

Secondary lesions: The "pintids" appear as macules or papules of varying number, color, and size, on uncovered parts of the body. The colors of the macules are, in order of frequency: bluish, white, grayish, violet, black, pinkish, yellow. A certain degree of parakeratosis and of prurigo is frequent.

Late lesions: These lesions are especially characterized by deep pigmentation associated with keratosis and dermic atrophy. The keratosis of palms and soles accompanied with dyschromia of the dorsal side of ankles and wrists are reminiscent of old cases of yaws. Aortic lesions have been found.

Prognosis: With the exception of the last mentioned lesions, the disease offers only esthetic inconveniences.

Diagnosis: The history and the morphology of the lesions distinguish the disease from syphilis and yaws. However, pintic keratosis greatly resembles the similar lesion in yaws.

The reaction of Bordet-Wassermann, negative in the first period of the disease, becomes more and more frequently positive later on (60 per cent during the second period, 100 per cent in advanced cases). The differential diagnosis with syphilis and yaws is therefore difficult. The research of the parasite in the lymph of active lesions can be attempted.

Treatment: The same as for syphilis or yaws.

5. TROPICAL ULCER*

Definition: Ulcers frequent in the tropics, clinically characterized by a grayish green gangrenous, adherent, somewhat filamentous layer covering the ulceration. Sometimes the necrotic extension is very pronounced on the surface as well as in the depth and the ulcer is really "phagedenic." In that case it resembles the "hospital gangrene" of former times. Bacteriologically, the extreme frequency of Vincent's association (fusiform bacilli and spirochetes) must be noted.

GEOGRAPHIC DISTRIBUTION

It is spread in all tropical regions where the affection is the predominant type of ulcers (in Indonesia 1,353 out of 1,805 ulcerations of the legs according to Keyzer). It is found especially in low and damp regions. Nevertheless in Central Africa, Ruanda Urundi, between 1,500 and 2,000 meters' elevation, is greatly affected. Epidemics broke out in North Africa in 1943.

Sometimes the disease presents an epidemic picture in certain settlements where general hygiene and food conditions are insufficient, and where means of taking care of small sores are lacking.

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* French, ulcère tropical, ulcère phagédénique.

ETIOLOGY

Barefoot walking is a prime causal factor. The disease is rare among Europeans who are more easily subject to ecthyma. The germ probably needs a slight traumatism in order to penetrate. Since Vincent's studies of hospital gangrene and ulcer, most authors are inclined to attribute a causal role to the association described by that author. The fusiform bacillus is a long organism (7 to 8 μ and more) with slightly pointed extremities, Gram-negative, showing a granular structure after staining, anaerobic and sometimes mobile. Certain writers admit its possible transformation in the cultures into spiral organisms. This eventuality seems incompatible with our general knowledge. Experiments with this germ are difficult and its etiologic role is still uncertain.

As to the *Spirochaeta* (*Borrelia*) *vincentis*, it is a thin spirochete, easily stained but pale and in loose spirals. Like the fusiform bacillus, this spirochete belongs to the buccal flora and is probably also present in sanguinolent spirochetal bronchitis. Vincent's association is found in Plaut-Vincent's angina, in ulcerous membranous stomatitis, and as surinfection in various oral lesions including the epitheliomas.

Certain attempts to inoculate the disease in man appear positive and the part played by contagion is not excluded.

The diet deficient in proteins, calcium, vitamins, often found among natives, is also incriminated.

PATHOLOGY

No unusual pathology is encountered. Sharp inflammation with large necrotic areas constitutes the fibrino-purulent putrefaction which covers the ulceration. The epithelium shows hyperacanthosis on the edges of the ulceration.

The acute and subacute inflammation (infiltration of the skin by plasmocytes and lymphocytes) is followed by fibrosis. Sometimes we note pseudo-epitheliomatous (acanthosis) or even real epitheliomatous lesions.

SYMPTOMATOLOGY

The patient ordinarily shows a well developed ulcer and it is rare that traces of the small accidental lesion or of the first vesicle can still be seen. The ulceration is 1 to 2 cm. in diameter, is covered with a thick, greenish, bloody layer of putrid odor, adhering to the bottom and of filamentous structure. Evidently there is a decomposition of cutaneous tissues. The ulcer spreads more or less in surface, keeping its oval or round form (except in places unfavorable to the geometric appearance, such as between the toes, etc.), and may attain several centimeters (or inches) in diameter. The extension in depth is ordinarily more moderate, the bottom is excavated, the edges infiltrated and projecting. Fever and adenopathy may be observed but the latter does not suppurate. Very phagedenic forms may bring to light tendons, bones, etc. Finally, the necrotic zone is eliminated and a tenacious ulcer remains. The latter may leave fragile scars, retractions, etc.

It is almost always localized on the lower part of the leg, on the feet or toes. In spite of the fact that the ulcer is considered contagious and autoinoculable, it is generally single. In fact these two eventualities are rarely observed.

Complications are rare. Epitheliomatous transformation has been noted (Nigeria) but seems very rare in the Congo.

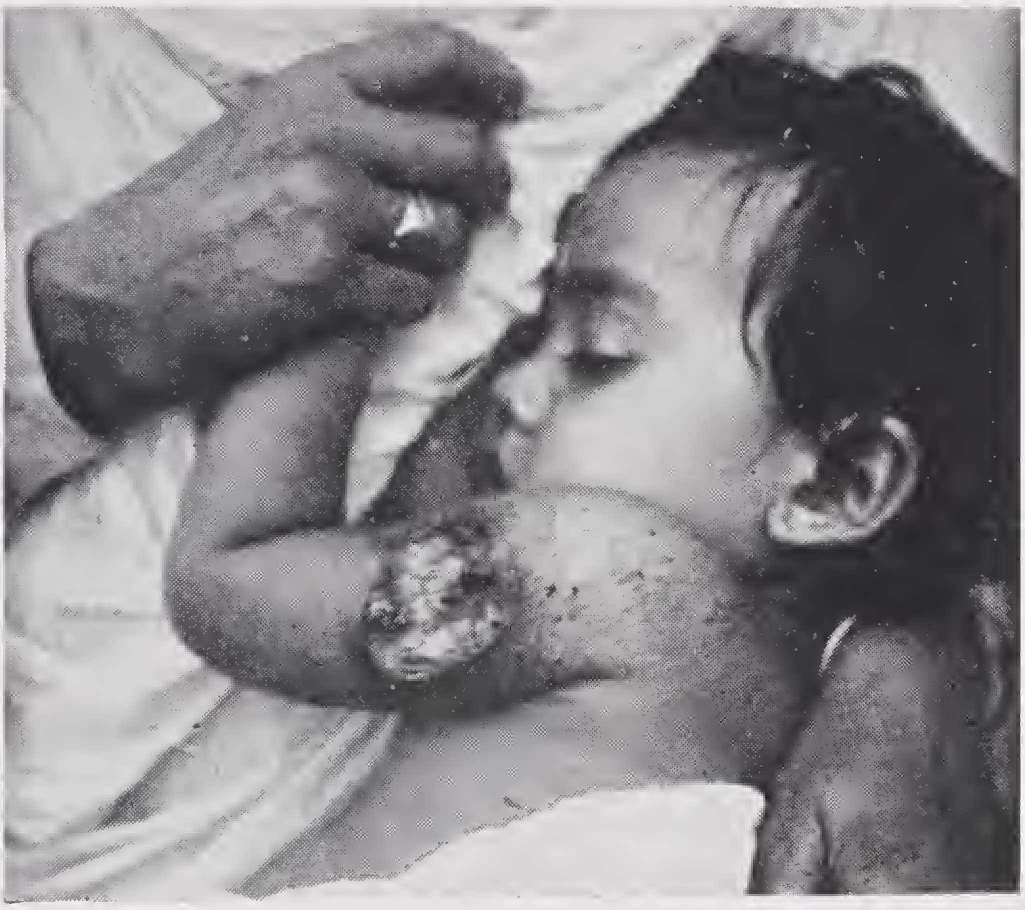

Fig. 65. Tropical Ulcer on Smallpox Vaccination Lesion
Courtesy Dr. E. P. Snijders, Indisch Instituut, Amsterdam

DIAGNOSIS

The appearance of the decomposed tissue covering the ulcer is typical. A microscopic examination is rarely necessary. It is made with Giemsa or with the black field condenser.

Syphilitic or pianic ulcers show a slower evolution and are preceded either by gummata (in this case with perpendicular edges) or a serpiginous type (tertiary ulcero-tubercular lesions). The Oriental sore is more indolent but is not confined only to the leg.

Primary yaws very rarely appears overinfected by the fuso-spirochetal combination and will in any event be diagnosed in the secondary period. Varicose ulcers are rare in natives and have a recognizable venous and cutaneous syndrome.

PROGNOSIS

Favorable from the life viewpoint, it is more reserved from the local. The ulcers exceeding 5 to 6 centimeters in diameter often leave very fragile scars. Cases having great phagedenism have a possible fatal prognosis but these patients are often already exhausted by other illnesses.

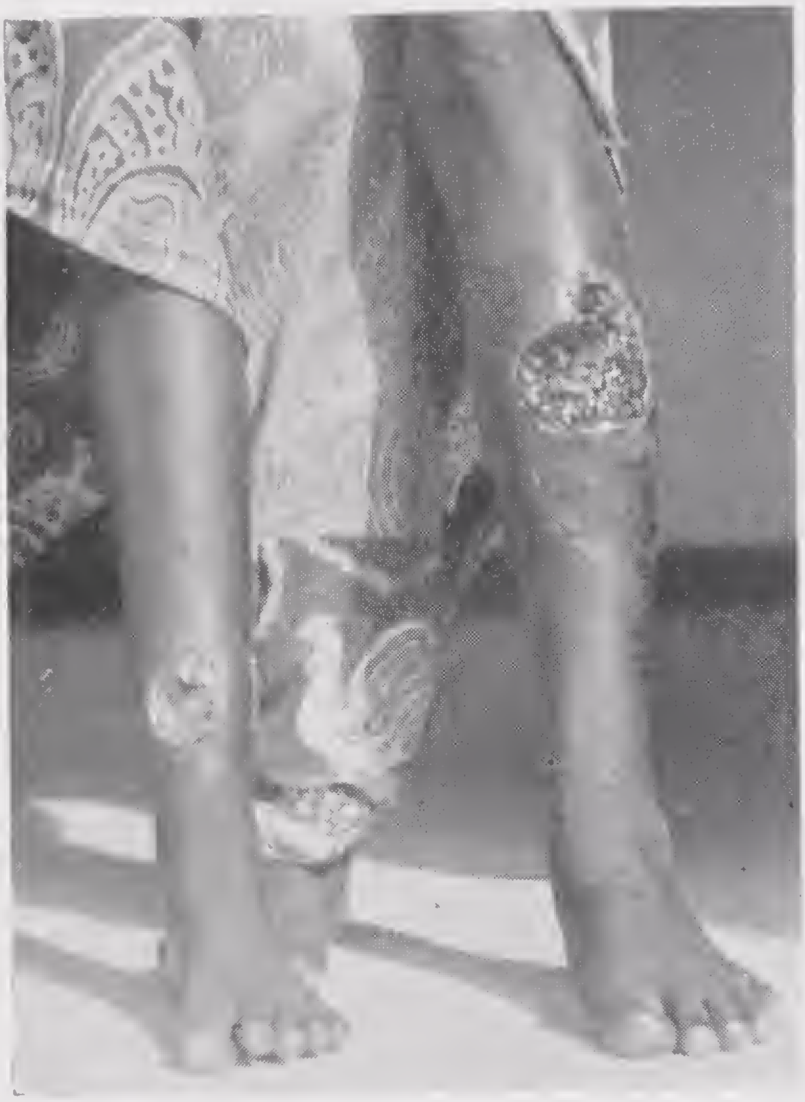

FIG. 66. COMMON SIGHT OF TROPICAL ULCERS IN THE CONGO (Phot. A. Fain, Tropical Institute, Antwerp)

TREATMENT

A rest in bed is always helpful. Serious cases may require a general tonic and anti-infectious treatment. The use of arsenobenzenes intravenously as well as locally has its partisans but does not seem indispensable to us. Many practitioners have also praised surgical intervention, curettage, even incisions, igneous or chemical cauterization, with object of removing the putrid matter, and followed by grafting. These methods are evidently rapid but necessitate anesthesia.

Experience shows that elimination of the decomposed area may be achieved at less cost by irrigation, followed by wet dressings. For the irrigation, corrosive sublimate 1 per thousand, or acriflavine 1 per thousand, is useful in daily dressings, or the endless variety of antiseptics: chlorated antiseptics, etc.

Still more active but also much more painful are hypertonic applications, the simplest being magnesium sulphate in crystals to be renewed daily for 4 to 5 consecutive days.

In one way or another the object is to cleanse the ulcer and to obtain a clear red bottom. Mechanical cleaning (swabs, superficial curettage) may help. This point having been reached, the filling in is easily obtained. Iodoform is often useful in spite of the possibility of cutaneous sensitization. Prescribe boric acid 9, iodoform 1. Any other antiseptic may be effective. Sulfonamides are not necessary but are very efficacious.

The tertiary period of epidermization will be the slowest: for this, use slightly antiseptic pomade: Peruvian balsam, oxide of zinc or, better still, adhesive plasters. At this stage dressings will be rare, at least if the patient can stay in bed.

More recently, the enclosure of the ulcers in plaster after a minute peeling, and dressings with waxed antiseptic gauze (sulfonamides) have been advocated. Penicillin appears also to be a general or local resource.

PROPHYLAXIS

Wearing shoes protects against primary lesions. It is important to assure early care of all small sores of the lower limbs. From this viewpoint a medical assistant must watch the laborers. Wholesome food is indispensable.

*Desert Sores**

This affection has been described in Northern Australia, South Africa, the Middle East, etc. It strikes desert regions and sometimes appears linked to infection by Loeffler's bacillus, which also causes concomitant epidemics of diphtherial pharyngitis.

Appearing at first either as a vesicle or an inflamed elevation, the lesion finally shows itself as an ulcer covered with a false grayish membrane. Bacteriologic isolation sometimes shows diphtheria bacilli (difficult to isolate in old cases), sometimes other germs (streptococci, etc.). Diphtherial paralysis may appear. The evolution is chronic.

Diagnosis must be made with ecthyma, the Oriental sore, bacterial anthrax (sharp development, vesiculo-necrotic appearance, etc.). It appears that various affections have been described under this name, particularly ecthyma.

Treatment must first be local: antiseptics, sulfonamides. If there is diphtherial infection, serum must be used in general and local injections (4,000 units on the periphery of the ulcer), and penicillin.

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* French, Ulcère du desert; Dutch, Veld sore.

Acute Gangrene of the Scrotum or Sexual Organs

Described in Europe by A. Fournier, this affection, especially the scrotal form, more rarely of the penis, is frequently met with in regions of Central Africa. On the scrotum, gangrene may be so rapid and so widespread that the testicles, entirely intact, are exposed. On the penis we note more or less extensive gangrenous ulcerations.

The disease is probably due to superinfection of small erosions, but the nature of the germ has not been established. Clinical knowledge points toward a similarity with tropical ulcer. Sulfonamides per os are useful in circumscribing the extension of eschars. Penicillin should be tried.

6. MUCOCUTANEOUS LEISHMANIASIS

Definition: A nodular and ulcerous disease caused by *Leishmania tropica* and affecting the skin and the mucous membranes of neighboring parts and mouth. Transmission is due to a Phlebotomus.

HISTORY

The Oriental sore has been recognized and well known since the eighteenth century. Russell in 1756 called it "Aleppo boil." The parasite was discovered only in 1903 by Wright in an ulcer of an Armenian child in Boston. It was first named *Helcosoma tropicum* but later recognized as belonging to the recently described genus Leishmania(see kala-azar). Nicolle in 1908 gave further confirmation of this when he cultivated the parasite and obtained the mobile Leptomonas forms. In Brazil Leishmanias were shortly afterwards found in "Ulcera de bauru" (1909), "buba braziliana" (1911), and "espundia" (Escomel, 1911).

GEOGRAPHIC DISTRIBUTION

Oriental sore (of Delhi, Alep, Bagdad, Biskra, etc.) is found in subdesert zones of the old world. The American muco-cutaneous "espundia" is limited to various South American distinctly wooded regions from Guiana to Paraguay. The disease is seen also in Central America. In Sao Paulo it forms 20 per cent of the dermatologic cases. It is also found in Egypt, North Africa, Nigeria, Tchad, etc.

ETIOLOGY

For the etiology of *L. tropica* we refer to the morphologically identical *L. donovani* and kala-azar. Both species can be separated on clinical and geographic ground but even more by the lack of cross immunity in man.

L. tropica confers a lifelong immunity. It is said that the Jews in Bagdad inoculated the scraping of Oriental sores on the legs of their children to protect them from scars in the face.

Some authors believe it advisable to retain the specific term *L. braziliensis* for the South American form. There is, however, no definite proof that the conditions are basically different in separate parts of the geographic distribution.

Men and also dogs are the most important reservoirs of *L. tropica.*

The Russian authors (Kojevnikow in particular, 1944) distinguish two types of cutaneous leishmaniasis. The first called *L. tarde exulcerans* is the dry type with long incubation (several months), late ulceration, slow evolution, and urban distribution. The parasites are numerous in the lesions and there is no known animal reservoir. The second type called *L. cito exulcerans* is the humid type with short incubation (a few weeks), rapid ulceration and lymphangitis and a rural desert distribution. The parasites are scarce. There is an animal reservoir in "gerbilles" (*Rhombomys opimus*) and "sousliks" (*Spermophilopsis leptodactylus*). The parasites are highly virulent for mice. Neither form confers cross immunity to man. These interesting facts should be investigated in other countries.

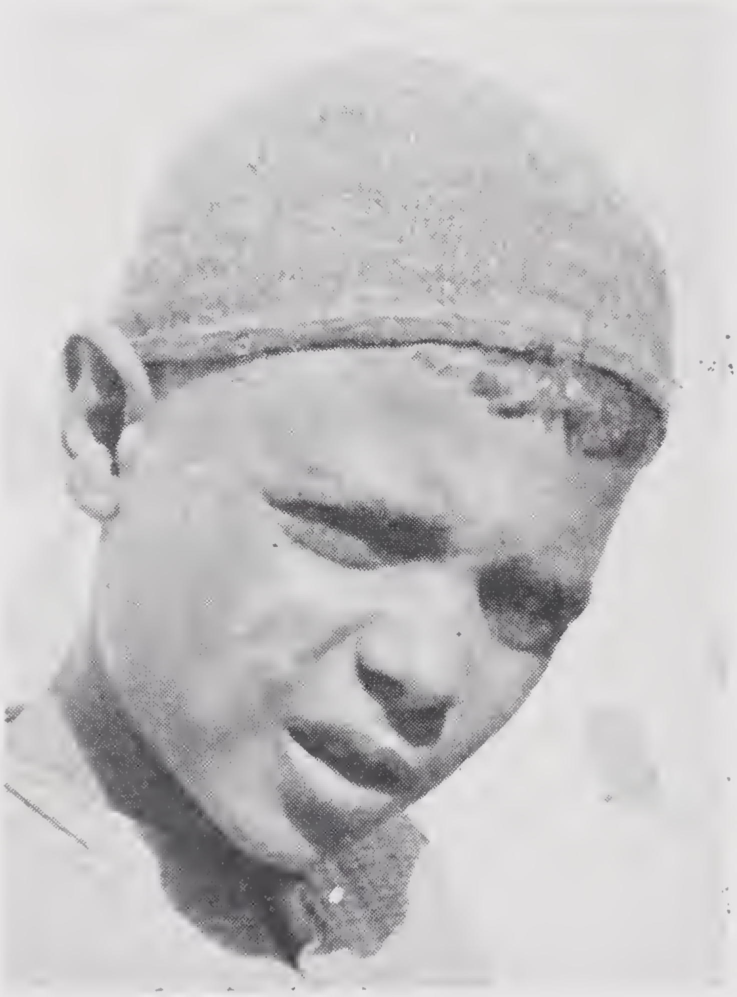

FIG. 67. ORIENTAL SORE FROM EGYPT
Infiltration. *Leishmania tropica* (L. van den Berghe)

TRANSMISSION

The role of the Phlebotomus in the transmission of cutaneous leishmaniasis had been suspected since 1905 (Pressat) and has since been amply proved: *Phlebotomus papatasii* and *P. perniciosus* in the Near East, *P. intermedius* in Brazil. Other insects and Arthropods such as

Stomoxis and *Hippobosca* flies, *Cimex, Trombicula,* and *Rhipicephalus* have been suspected as having a role in transmission. It seems, however, that *Phlebotomus* are, in all geographic sites, the dominant vectors. The biology of the sandflies has been dealt with in the section on kala-azar.

PATHOLOGY

At the papulous stage we note dermatic granulation rich in plasmocytes, lymphocytes, histocytes. Some of the latter are packed with intracellular Leishmanias. During the period of ulceration, the inflammation is more exudative, and richer in polynuclear cells and finally, fibrous scars dominate. On the mucous membranes especially, superadded infections often modify the anatomic appearance in a more inflammatory and ulcerous necrotic sense.

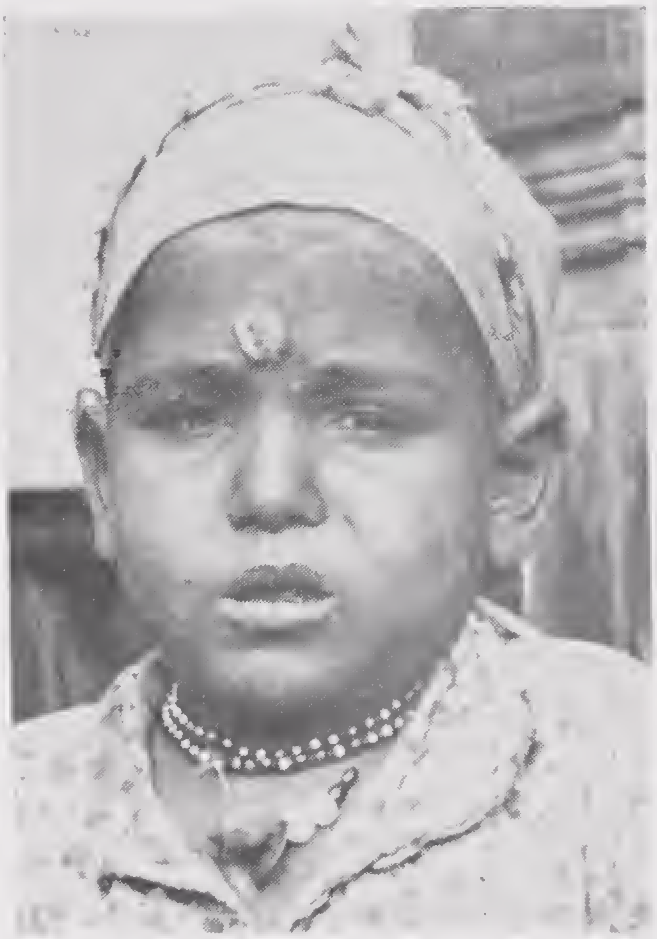

FIG. 68. ORIENTAL SORE FROM EGYPT
Ulceration. *Leishmania tropica* (L. van den Berghe)

SYMPTOMATOLOGY

1. *Cutaneous form:* Incubation is of highly variable length: between several days to several months. The malady begins with a papule which grows continually until reaching a dimension of 2 to 3 cm. This element may become sclerous without ulceration but more often, however, a scabby ulceration appears and grows in extent, sometimes with a serpigenous appearance, although remaining superficial. Its location is in exposed areas, often on the face. In Yucatan (Mexico) the ears are easily affected, and local mutilations follow ("chicleros ulcers").

The number of lesions varies, sometimes single, sometimes numerous, ordinarily 2 to 3. Lymphangial nodules in ulcerous forms have been noted in Panama, Central Asia, etc. General health is not greatly affected.

2. *Muco-cutaneous form:* Although in South America, as elsewhere purely cutaneous lesions predominate, it is especially in that part of the world that we find with great frequence (20 per cent) an extension to the buccal, nasal, and pharyngeal mucous membranes. This fact justifies the special name: South American or muco-cutanous form.

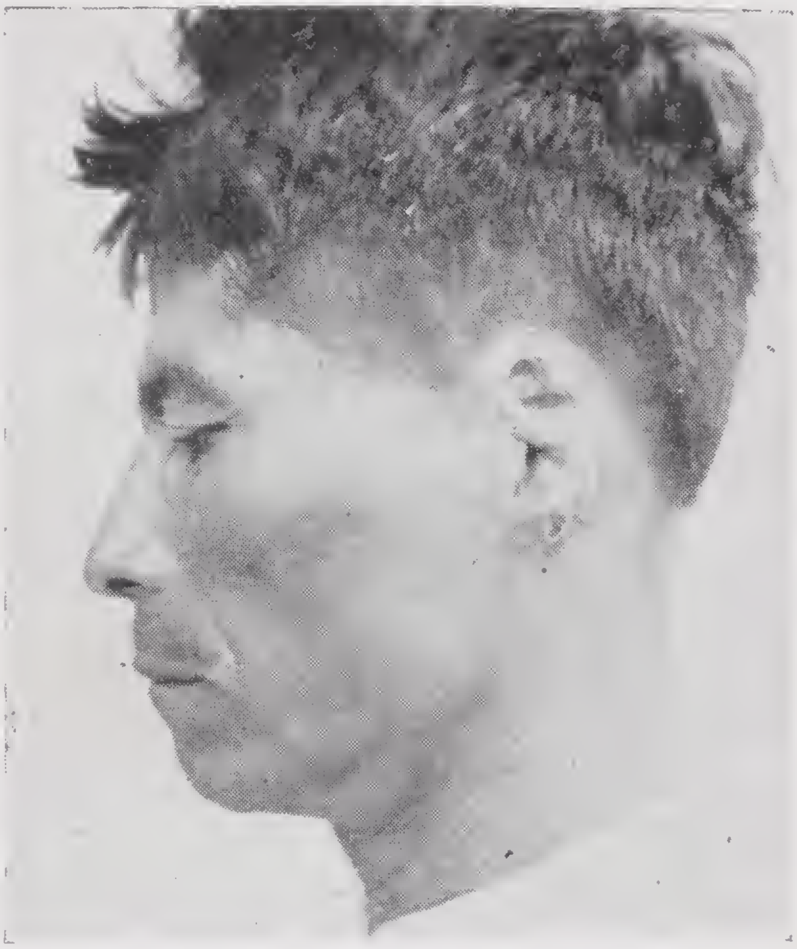

Fig. 69. Leishmaniasis of the "Chiclero"
Case of Yucatan, Mexico, with lesions on the left ear (courtesy Dr. E. Brumpt)

This aspect of the disease does not differ greatly from the cutaneous form. A papule starting near the middle of the face ulcerates slowly then gradually spreads to the nose, the mouth, the pharynx, ending with great loss of substance and finally heals.

The influence on the respiratory and digestive functions is comprehensible and the general state of health may be seriously affected. It is needless to say that this form of the disease is extremely disfiguring.

PROGNOSIS

Oriental sore has a very favorable vital prognosis but is often very unaesthetic. The prognosis of the muco-cutaneous form is more difficult not only from the vital but also from the functional and aesthetic viewpoint.

DIAGNOSIS

Clinically, it would be difficult were it not for the knowledge of its endemicity. Confusion is possible with diverse papulo-ulcerative dermatoses (syphilis, yaws, mycoses). Lesions of the mucous membranes may be taken for yaws (gangosa), syphilis, lupus, etc.

The Bordet-Wassermann reaction will direct the diagnosis toward syphilis or yaws. The microscope will prove of great utility. Scraping the nonulcerous papulous areas (by pressing the tissues in order to obtain dermic secretions but not blood), or also by puncturing the healthy skin of nonulcerated parts will generally show the Leishmanias (use prolonged Giemsa staining).

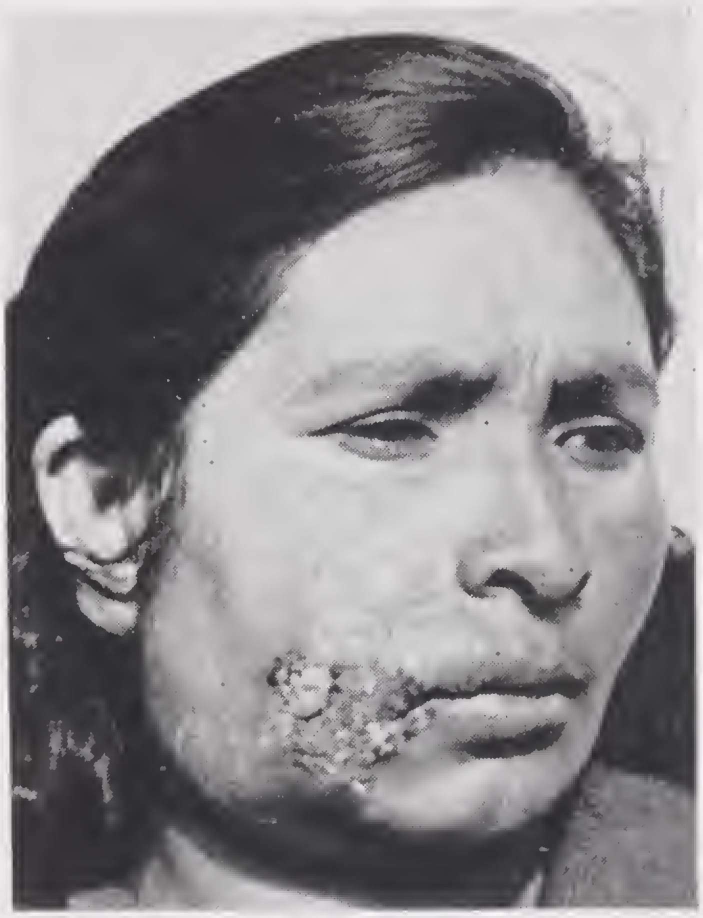

FIG. 70. AMERICAN LEISHMANIASIS
Affecting the skin and mucous membranes of the mouth (courtesy Dr. Romaña, Brazil)

Cultures on a blood medium may be especially useful but require lesions that are not overly infected. Penicillin added to the culture medium may facilitate the isolation by inhibiting the microbial development.

TREATMENT

Antimony, either trivalent or pentavalent, may be active but is not always so (Neostibosan, etc.). Sulphate of berberine: 2 cc. in 1 per cent solution injected into the edges of the ulcers. Locally: carbonic snow, antiseptics (methylene blue, etc.) are useful. In Asiatic Russia an infiltration of the lesions with a solution of atabrin of 3 to 5 per cent, with an application of atabrin pomade 10 per cent on the ulcers, has been commended.

Prophylaxis: The protection of the sores by dressing is imperative to prevent flies and insects being infected on them. The use of special mosquito nets and repellents are recommended in areas where the disease is endemic (see visceral leishmaniasis).

7. GRANULOMA VENEREUM*

Definition: An ulcerous disease of venereal origin, of very chronic development and located in the genito-crural or perineal region. Its etiology is uncertain.

Geographic Distribution: It is found in numerous tropical regions of the old and the new world, India, New Guinea, Africa, Guiana, Brazil, southern states of the U.S.A. It has been noticed in the Congo.

Etiology: Its predilection for the colored race is notable (particularly for black-skinned), Melanesians, Africans, Afro-Americans, Dravidians. However, the whites are not exempted.

In 1905 Donovan described an intracellular bacilliform organism which, according to certain writers, may be related to Friedlander's bacillus and, like it, easily cultivated, while others claim it will not develop on artificial medium. In all events the culture obtained (*Klebsiella granulomatis*) are not pathogenic and from this fact a virus has been incriminated, possibly related to the bacilli whose pathogenic role is poorly established.

Venereal transmission seems to predominate.

Pathology: The infiltration of the granuloma is composed mainly of lymphocytes and plasmocytes with groups of polynuclears, it is characterized by the presence of vacuolated histocytes in which we can stain the Donovan's bacillary formations (Giemsa, silver impregnation). It can be compared to the histologic appearance of rhinoscleroma. Both have a marked tendency to fibrosis. The histologic aspect of the granuloma lends itself to a diagnosis of very great probability (groups of polynuclears, bacilliferous histocytes, proliferative epithelium).

Symptomatology: After an incubation varying from a few days to several weeks, the affection begins with an ulcerous papule most frequently located on the genital organs. Its superficial, then sclerous extension will bring on notable disorders, gradually gaining the entire perigenital area, sometimes partially destroying the penis, causing recto-vaginal fistulae, shrinkage of the urethra, etc. The lymph nodes remain exempt.

Prognosis is serious from a local viewpoint.

Diagnosis: New lesions or those remaining closed in the female genital organs are rather difficult to diagnose clinically: syphilis, chancroid, tumors, late ulcerous lesions of lymphogranuloma inguinale, etc. The chancroid and lymphogranuloma (the former always, the latter frequently) have a considerable glandular repercussion. The Bordet-Wassermann reaction, or Frei's test, can be used to fix the diagnosis. The Donovan's bodies (Giemsa) should be investigated. Histology will also be of value in distinguishing the granuloma from tumors, lupus, etc.

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* Synonym: Granuloma inguinale.

Old and extended lesions with their combination of ulceration and cicatrization are easy to diagnose.

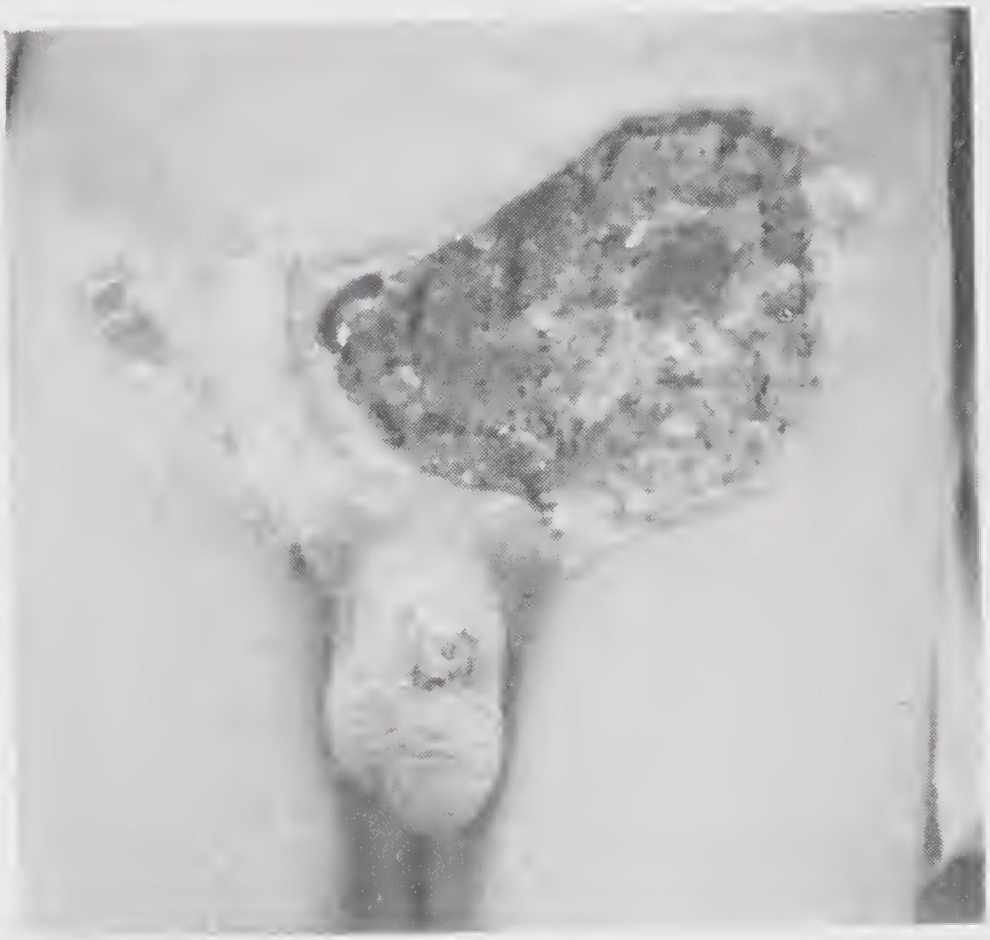

FIG. 71. GRANULOMA VENEREUM
Case from Venezuela (courtesy Dr. E. Brumpt)

Treatment: Antimony is recommended by many observers (Emetic, Fouadine, see: Sleeping Sickness and Schistosomiasis). Sulfonamides have also been used. Local treatment is ordinary. Streptomycin is active.

Rhinoscleroma

This affection, very similar in appearance, and in which a bacillus of the Friedlander type (Frisch's bacillus) has been isolated, is not especially tropical. The infiltrative lesion, very hard (intense fibrosis), lightly ulcerous, attacks especially the nose, the mouth, pharynx, and the trachea. It is possible to confuse it with syphilis, yaws, leishmaniasis, cancer, etc.

8. LYMPHOGRANULOMA INGUINALE*

This affection is fairly frequent in the tropics without being confined to them.

The etiology is attributed to a virus (Hellerström and Wassen), transmissible to the monkey by subcutaneous means, and producing in mice an encephalitis by introcerebral inoculation. This virus which measures about 150 $\mu\mu$ has been cultivated on chicken embryo.

Anatomically, adenitis shows necrotic foci surrounded by the epithelioid cells and Langhans cells, then a lymphocytic and plasmocytic crown. The cells of the exudation show small inclusions found also outside of the cell. Certain writers had previously identified them as Rickettsias.

The histologic appearance of the adenitis reminds one of the lesions of tularemia. With the exception of the lymph nodes, the infiltration and the consecutive sclerosis are as usual.

Clinically, the small primary ulcerous lesion often escapes examination (genital site). In a few weeks a subacute adenopathy follows, with more or less general disturbances, which finally suppurates lightly, forming multiple and lasting fistulae. Often deep-seated lymph nodes (iliac) are affected.

In man the infection of the lymph nodes may bring on a more or less elephantoid condition. In women, the inguinal bubo is rarely seen but rather an inflammation of the pelvic glands, stubborn vulvo-vaginal ulcerations, infiltrations of the rectum with final shrinkage. This "genito-ano-rectal" syndrome is sometimes accompanied by elephantoid lesions of the vulva, constituting the "vulvary esthiomene" described by Huguier in 1848 and including a chronic state of elephantiasis, a vulvular ulceration and ano-proctitis. Fournier had attributed the rectal syndrome to syphilis. Ano-rectal syndromes are also found in men.

The "quoad vitam" prognosis is favorable but serious locally in women.

Diagnosis must be made with other adenites of syphilis, of chancroid, of ordinary infection, of plague. The case history, the knowledge of the ways of infection, the appearance of the suppuration, sometimes the lymph node biopsy, will facilitate the diagnosis. Frei's test (cuti-reaction with natural or experimental killed virus) gives a more certain indication.

On the vulva, the hardness of the infiltration and the callous nature of the ulcerations, the appearance in turgescent "cox-comb" of the small lips will attract notice.

The treatment, previously very unsatisfactory (antimony, copper, gold, etc.), has been renovated by the use of sulfonamides.

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* Synonyms: Venereal Lymphopathy, Nicolas-Favre disease, Climatic Bubo.

9. MISCELLANEOUS DERMATOSES

Keloids

The marked tendency of Negroes to have Keloid scars deserves attention.

By the use of a precise and repeated technic, racial raised tattooing is obtained. Formerly very common in Central Africa, it now tends to fall into disuse, at least on the face. Involuntarily, often after burnings, etc., abundant keloids appear. The same facts are noted among the population of Oceania.

Aseptic surgery rarely causes these recidivous hypertrophic fibrous reactions.

The favorite localization of syphilids on these formations (racial tattooing) has been noticed.

Ainhum

Rosser attributed the Keloids and elephantiasis to a fibro-plastic diathesis special to Negroes. Ainhum is attributed to the same disposition.

It is a fibrous ring appearing on the under surface of the little toe and finally pediculizing and separating the toe, whose skeleton undergoes localized atrophy.

The etiology is obscure; the racial tendency and going barefoot are the main apparent factors. Treatment is surgical.

*Lichen Tropicus (Prickly Heat)**

Definition: Very common dermatosis in warm and humid climates. It is related with heavy sudation and characterized by an itch and papulo-vesiculous eruption.

Geographic Distribution: It is found everywhere in the tropics.

Etiology: Microbes (staphylococci) and fungi have been incriminated but these organisms appear as contaminations on pre-existing lesions.

Sudation plays an important role. The type of clothing intervenes also. The old-fashioned flannel belt was responsible for many local eruptions. The natives in the Congo, who never have prickly heat when they wear few clothes, develop the condition when they wear a tight uniform. Obese persons, blonde individuals, and children are more susceptible.

Pathology: The sweat glands are blocked by swollen or desquamated cells.

Symptomatology: Small red papules, often with small vesicles, are mostly found around the belt, on the shoulders, but also on other parts of the skin. Itching is very intense. The condition ends with thin desquamation. Staphylococci may complicate the disease.

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* French, Bourbouille; German, Roter hund.

Treatment: After a bath with antiseptic soap, the skin should be carefully dried. Apply a salicylated alcohol lotion 2 per cent, then powder with talc and zinc oxide, eventually with camphor, menthol, etc.

Prophylaxis: Avoid heavy sudation and tight clothing. Change underwear frequently and use porous materials. The skin must be aerated as much as possible. Tepid showers twice a day. Avoid sea bathing. Air conditioning is desirable.

10. TROPICAL PURULENT MYOSITIS

This disease has been related before to filariasis. Its etiology seems staphylococcic but the mechanism of the localization of the microbes in the muscles is not known.*

Purulent myositis is commonly encountered in warm and humid countries, especially among native laborers. In the Congo its distribution is irregular.

The clinical picture is variable. The severity of the condition varies from a moderate feverish state to very grave toxi-infectious phenomena.

The tumefaction of one or several large muscles (mostly in succession) leads to subacute abscesses producing a reddish and not very abundant pus, or, more rarely, common pus.

The prognosis is variable and was very severe before modern chemotherapy limited the extension of the cases.

The diagnosis is not always easy, the muscular tumefaction being sometimes discrete and the disease appearing then as an influenza.

The treatment uses sulfonamides with the necessary surgical steps. Penicillin should be tried.

11. FILARIASIS†

From the viewpoint of pathogenesis, we will consider a series of syndromes of increasing gravity and importance, all due to Nematodes belonging to the superfamily of the Filaroidea, and commonly called Filaria.

(A) MANSONELLA OZZARDI

History: First obtained by Ozzard from Carib Indians in British Guiana and described by Manson.

Geographic Distribution: West Indies, Central and South America.

Morphology: The adults are found in body cavities and omental tissues.

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* Leptospira have been incriminated without sufficient proof.

† French: Filariose, Filariasis.

The male has a strongly curved caudal extremity. The female measures 65 to 80 mm. in length. The microfilaria, 175–240 μ by 4–5 μ, is found in the blood. It is a nonperiodic sheathless microfilaria and has a sharp tail.

Transmission occurs by *Culicoides furens* (Buckley, 1934) and possibly *C. paraensis*.

Pathology and Symptomatology have been inadequately studied but seem insignificant.

(B) ACANTHOCHEILONEMA PERSTANS

History: The worm was first found by Daniels (1898) in aborigines of British Guiana, then described by Manson who found the microfilaria in the blood of Congo natives.

Geographic Distribution: Common in most of the African territory from Algiers and Tunis to Northern Rhodesia, it is frequently associated with Loa loa in west and central Africa. *A. perstans* is also found in Panama, Trinidad, the West Indies, and South America from Venezuela to the Argentine.

Morphology: The adults live in the body cavities: mostly peritoneal, rarely pleural and pericardial. They are elongated, white Filariae with a smooth cuticula and strongly incurved tails in both sexes. The male measures approximately 45 mm. to 60 mm. and the female 70 to 80 mm. by 120 μ. The microfilariae, although nonperiodic, appear fewer in the peripheral blood in the daytime than at night. They are small, measure from 100 to 200 μ by 4.5 μ, unsheathed, and with abruptly rounded tails.

Transmission: In hyperendemic regions of Central Africa, almost 100 per cent of the adults harbor the parasite. The epidemiology of *A. perstans* has never been adequately studied. Human infection is said generally to be produced by bites of *Culicoides austeni* (Sharp, 1928), a small midge which bites voraciously at dusk and night and lays eggs in shallow waters. The adults emerge after three days from the larvae. One wonders, however, if the role of transmission by Culicoides might be accepted as certain since we know more about other closely related and widely found species of *Acanthocheilonema*, such as *A. streptocerca* (see further) and *A. vanhoofi*. The latter species, according to Peel and Chardome (1946), is responsible for the so-called perstans microfilaria of the chimpanzee in the Congo.

Pathology and Symptomatology: Allergic cutaneous phenomena have been attributed to the antigen liberated by the numerous living or dead perstans microfilariae. This has not been definitely proved. On better grounds, however, *A. perstans* has been incriminated as being largely responsible for the eosinophilia so widely found among natives.

(C) ACANTHOCHEILONEMA STREPTOCERCA

History: The microfilaria was described by Macfie and Corson (1922) from the

Gold Coast, being present in the derm from as many as 45 per cent of villagers. Dubois found it in Congo natives (1933). Streptocerca microfilaria are fairly common in the region as well in man as in the chimpanzee. Two complete female specimens have been recently recovered from this ape (Peel and Chardome, 1946).

Geographic Distribution: West and Central Africa.

Morphology: The male is not known. The females recovered from the skin of a chimpanzee (*Pan paniscus*) in the Congo, measured 27 mm. in length. The microfilariae seen in utero and some of them coming out of the genital pores had the same morphology as the one obtained from the derm of 5 out of 11 chimpanzees and from the derm of men. The streptocerca microfilaria has no sheath, is found only in the derm, and measures 240 μ by 3 μ. The cuticula is transversely striated. Nuclei are seen in single line to within 1 μ of the caudal tip.

Transmission: So far not known, possibly by *Culicoides* (see above, *A. perstans*).

Pathology and Symptomatology: This has been studied but little and *A. streptocerca* may play a greater role in filarial pathology than is supposed. Dubois and Vitale in Nepoko (Belgian Congo) have found streptocerca microfilaria in 31 out of 34 skin biopsies from elephantiasis of the lower limbs.

(D) LOA LOA

History: The worm was extracted in 1770 by Mongin from the eye of a Negress in St. Domingo. The "eye worm" was often seen among newly imported African slaves. It was first reported from Africa in 1777.

Geographic Distribution: Confined to West and Central Africa, where in certain regions it is extremely frequent among the natives and Europeans.

Morphology: Whitish threadlike worms with small bosses on the cuticle. The male measures 30–35 mm. by 0.35–0.45 mm. and the female 50–70 mm. by 0.5 mm. The blood microfilaria is sheathed, has a diurnal periodicity and measures 275 μ by 8 μ.

Transmission: Chrysops dimidiata and *C. silacea,* day-biting Tabanid flies, act as intermediate hosts. The females only feed on blood. The larval stages of Loa loa are found in the thoracic muscles, connective tissue, and fat body of the flies. In human hosts, the infective larva enters connective tissue and develops very slowly. The adult worms migrate for many years (10 years and more in the connective tissues).

Pathology and Symptomatology: Loa loa has a fairly decided pathologic role. None of the symptoms are attributed to the introduction of larvae. The adult in itself seems inoffensive. As a matter of fact, it is sometimes observed where the skin is delicate or under bulbar conjunctiva and even on the surface of operatory incisions. The total absence of reaction in the course of this migration is striking. Even in the conjunctiva there are hardly any but slight subjective phenomena, a sensation of foreign bodies and at times a very slight redness. We have never come across the "maddening pain" quoted by Elliot.

Eosinophilia is, on the contrary, regular and very strong (20 to 60 per cent) and probably in relation with the proteins of the worm.

Besides this, one observes an individualized manifestation occurring very frequently in white people and more seldom in natives, and known since 1895 (Argyll Robertson) under the name of Calabar Swellings. This name which alludes to the frequency of swellings in resident Europeans in Southern Nigeria can be called "erratic filarian edema."

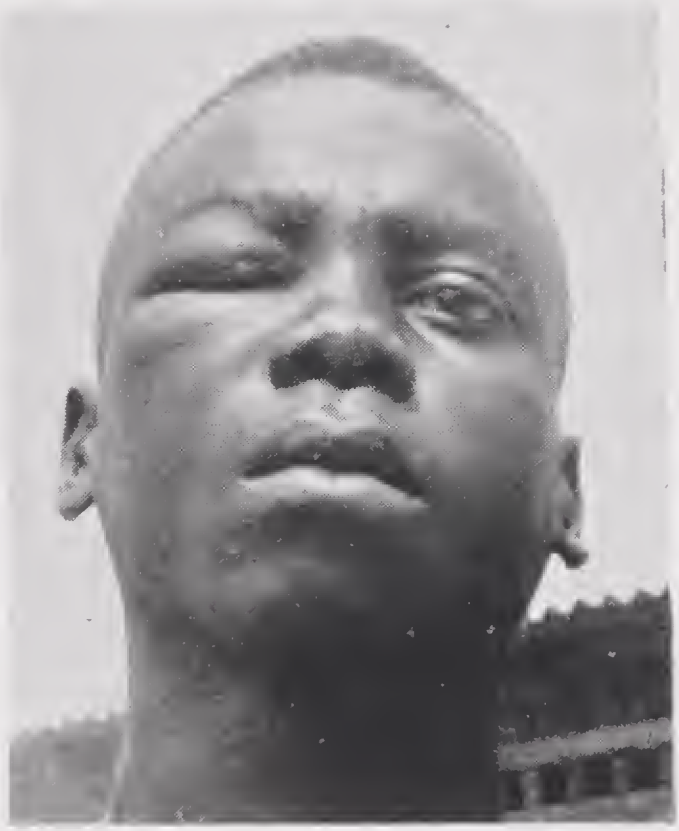

Fig. 72. Loa Loa Case: Swollen Eye Lids
Compare with the Romaña's sign in Chagas disease (phot. Van Breuseghem, Tropical Institute, Antwerp)

Calabar Swellings are moderate, elastic, without the skin depression phenomenon, not painful or red, but sometimes pruriginous and eventually giving an impression of tension or, if in the feet, making walking very difficult. They can be located at any site on the cutaneous surface, with a predilection for the anterior side of the wrist, thenar or hypothenar eminences, rarely on the scrotum and even more seldom on the buccal or glottic mucous membrane. These edemas are less erratic than their name leads one to believe. It is rare for them not to persist for two or three days or even longer. Sometimes there is a very persistent state of edema.

Prognosis: This, however, remains very slight. The condition, in fact, is more of a discomfort and disfiguring to the face than a disease.

Pathogenesis: The pathogenesis of the edemas has been frequently discussed. The edema of Quincke is attributed to venous spasms. Observation has proved that the worm in itself and in its normal state is not a generator of edema. Besides, the writers who have tried to find adults on the level of edematic zones have not been successful. It is quite possible that after the death of a parasite other manifestations come to light, but it is hard to believe in the existence of a dead worm in every attack of edema. Microfilariae in the blood are often absent in those affected by Calabar Swellings. The most acceptable explanation of the manifestations has been connected with allergy to filarian proteins. This results particularly when the antigen of a worm breaks during extraction or in the course of experiments in which an extract of filaria is injected into the skin. Reactions of the "Calabar Swellings" type are produced in this way (Chandler, Gilis and Schubardt, Fairley, Rodhain and Dubois).

This agrees fairly well with the rather long "incubation" of the Calabar Swellings (several months) and their disappearance in the long run (four to five years) when the sensitiveness diminishes. Rodhain sets forth the hypothesis that the very light infections are the most allergic. This would explain how rarely the microfilariae can be discovered in the blood of these cases.

Other Symptoms: Urticaria has been observed fairly often. This is a dermic phenomenon, filarian edema being hypodermic. Neuralgia has also been pointed out, due perhaps to edema of the sheath of the nerves. Sometimes a pachydermic condition of the skin persists. Finally, certain writers (Stephanopoulo, Dubois, and Valcke) blame Loa loa for causing prurigo, but without having been able to furnish any other proof up to the present, but the rather doubtful "cum hoc ergo propter hoc." This manifestation would considerably aggravate the prognosis of the helminthiasis. Besides, it seems rather rare among the numerous carriers.

Diagnosis: Loa loa is an obvious consideration in the presence of Calabar Swellings, especially if endemicity can be accounted for. It would be very easy to confuse it with the edema of Quincke which is also attributed to allergia. This has a more varied distribution than the filarian edema, particularly the laryngeal edema which is more common (170 cases quoted by Koenig in 1924, of which 21 per cent died). Various lesions of the mucous membranes, even the deeply located ones, oliguric crises followed by polyuria, headache, and various cerebral disorders are also especially characteristic of the edema of Quincke. The constitutional hereditary basis is also more apparent. In fact, the diagnosis to be made is that of the allergene involved and not that of the syndrome.

The discovery of the adult worm (by no means regular), of the blood microfilariae (often missing), and of a strong eosinophilia (regular) will prove decisive or probable elements. The immunity tests, cuti-reaction or deviation of the complement (Fairley) have only a group value. One generally utilizes, therefore, an extract of *Dirofilaria immitis* of the dog, which constitutes an abundant and aseptic material.

Treatment has been unsatisfactory. Adrenaline or more recent substitutes, also calcium, can be used in the course of laryngeal accidents, etc. Emetine and antimony have been prescribed with relative success. The treatment of prurigo is not satisfactory (anti-pruriginous products, autohemotherapy, etc.). The treatment of this filariasis must be directed in the anti-allergic sense.

Perhaps a cautious attempt at immunization with filarian extract is advisable. The anti-histaminics also deserve to be experimented with.

(E) WUCHERERIA BANCROFTI

History

Demarquay first discovered microfilariae in hydrocele fluid (1863) and Wucherer in Brazil found the same in chylous urine (Brazil, 1866). These larvae were first seen in the peripheral blood by Lewis in India (1872), while the adult female worms were recovered by Bancroft in Brisbane (1876). Manson described the nocturnal periodicity of the microfilariae in the blood and their diurnal concentration in the lungs. He also demonstrated that *Culex fatigans* was an intermediate host (1878). Manson-Bahr (1912) and O'Connor (1923) pointed out that in Polynesia norturnal periodicity did not occur.

Geographic Distribution: W. bancrofti is found in almost all warm regions of the world: The Near East, around the coast of Arabia, North, West, and Central Africa, Madagascar, India, the Far East up to southern and northeastern Australia, the Pacific islands, the Greater and Lesser Antilles and along the coast of northern South America. In the Southern U.S.A. (Charleston) cases were formerly found, originally imported with the slaves, and susceptible mosquitoes were infected. Until recently, *W. bancrofti* was considered as absent in the Congo and French Equatorial Africa. However, a focus has been discovered in the lower Congo and Kwango in the last few years (Henrard and Wanson, Fain).

Etiology

The threadlike adult worms are found tightly coiled in dilatations of lymphatics in man, who is the only known definite host. The male is 25 to 40 mm. long and about 0.1 mm. thick. The female varies in length from 50 to 100 mm. and from 0.2 to 0.3 mm. in width. The embryos at birth are surrounded by a delicate membrane representing the egg shell, which adapts itself to the elongate form of the body and is then called a "sheath." The sheathed microfilaria measures 300 μ by 8 μ. Its periodicity, which is generally nocturnal in the peripheral blood (mostly between 10 P.M. and 2 A.M.) but is not marked in the Philippines and in Polynesia, has not yet been satisfactorily explained.

Transmission

Several mosquitoes act as intermediate hosts in transmission. They belong to the genera Culex, Aedes, Anopheles, and Mansonia. It seems probable that all mosquitoes which are predominantly anthropophilic might be found to be appropriate hosts. The microfilariae escape from their sheaths in the stomach of the mosquito soon after an infective meal.

Within twenty-four hours they migrate from the stomach to the thoracic muscles, where they become sausage-shaped and quiescent, measuring from 125 to 250 μ in length by 10 to 20 μ in diameter. After approximately a week, a mould takes place and the larvae rapidly elongate into a third stage mature form which measures 1.5 to 2 mm. by 20 to 25 μ. These infective larvae migrate chiefly toward the head. They penetrate into the labium, and when the mosquito feeds, they burst their way through the thin membrane of this organ ("Dutton's membrane") and enter the skin by active penetration.

The complete development in the mosquito takes from twelve to twenty days. After penetrating the human skin the infective stage larvae pass into the lymphatics, where they settle, reach maturity, and mate. The first microfilariae are discharged and appear in peripheral blood in twelve months or more.

Pathogenesis and Pathology

It is unquestionable that among numerous subjects infected with *W. bancrofti* there are some without any appreciable symptoms, which, nevertheless, does not exclude a few lesions. These are due to the adult worm whose habitat is endolymphatic and which acts as an irritant substance in the interior of the lymph vessels and doubtless more especially if the worm is dead. This results in lesions of obstructive endolymphangitis which sufficiently explain the phenomena of lymphatic stasis and probably by this one fact, elephantiasis (experiences of Drinker on the dog).

However, acute inflammatory and toxi-infectious phenomena are observed in filaria carriers, the etiology of which remains a much discussed subject. Purely "filarist" writers consider that in this case allergy intervenes, due to the proteins of the worm (O'Connor). The "microbists," on the contrary, believe in the intervention of the streptococci, etc. (Drinker has shown that provoked lymphatic stasis makes the dog susceptible to local streptococcic infections, but this susceptibility appears rather as an effect than as a pathogenic cause.) Inside the lymphatic vessel, the filaria causes endothelial proliferation, more or less blocking the light of the vessel and causing stasis. If the parasite dies, the inflammation becomes more intense and obstructive thrombolymphangitis is produced. Recently, American observers have biopsied early cases involving soldiers of the Pacific Theater. They remarked lymphangitis, thickening and eosinophilic infiltration of the wall, central thrombosis with agglomerated, pyknotic eosinophiles, regardless of the presence or absence of worms.

The lymph nodes show follicular hyperplasia, edema, and eosinophilic infiltration, with or without worms.

Subsequently, the reaction, generally as a result of dead filariae, takes on a granulomatous appearance, epitheloid with a lympho-plasmocytic crown (tuberculoid lesion) and giant cells of foreign bodies. The center may later become calcified or sclerotic and all trace of the worm disappear. The lymphatic stasis, which is the consequence of these obstructions, intervenes in the origination of accidents described clinically (lymphatic varix, chyluria, etc.). The lymph nodes are the seat of similar lesions. In fact the worms live in the lymphatic vessels, both inside and outside the lymph nodes. The lesions are everywhere identical: lymphocytic infiltrate, eosinophilia around the dead worms and sometimes an extensive fibrosis of the lymph nodes. Local or blood eosinophilia is also observed. The early appearance of fugacious lesions with edema, vascular stasis, local eosinophilia are attributed to allergy against proteins of the worm. The frequent juxta-inguinal seat of the worms explains the abundance of funicular and epididymotesticular lesions.

Symptomatology

Asymptomatic cases seem numerous. The incubation is often rather slow, about a year, though quite recently American observers have noticed symptoms in the three months following the entry into the endemic zone. The first appearance of symptoms has been recently described under these conditions and in spite of the frequent absence of microfilariae in the blood, the diagnosis seems unquestionable. The clinical appearance, the histologic aspect of the biopsies and, above all, the discovery of adult worms in a part of the cases justifies the diagnosis made by these writers. The symptoms which were first observed showed, after a vague discomfort (heaviness in one of the limbs):

1. Slight lymphangitis, especially in the limbs, with moderate fever and sometimes centrifugal around the lymph nodes.
2. Often funiculites or epididymites, generally unilateral, with puffiness of the organs and at times thickening of the deferent duct.
3. Other subjects showed a fairly slight although generalized adenopathy with at times lymphatic nodules in unusual positions. Swelling of the epitrochlea ganglion is frequent.
4. Part of these subjects merely suffered from discomfort, heaviness of pains in the limbs, the testicles, etc.

Psychic symptoms obviously appear. The confirmed classic symptoms of Bancroft's filariasis have been divided into two groups: inflammatory and obstructive, both being related. Among the former, the most frequent seems to be *recurring endemic lymphangitis*. It is a lymphangitic, tronculary or reticulary thrust, accompanied by general toxi-infectious phenomena, at times very marked (cephalalgia, vertigo, vomiting, constipation, high fever), at other times milder (moderate fever). The fever episode may last several days, the lymphatic vessels may become hardened and voluminous. Such attacks may by repetition lead to elephantiasis with persistence of edema at every thrust (hence the name, elephantoid fever).

In certain cases only general phenomena exist, with the clinical picture of pure Filarian Fever, a condition very difficult to diagnose. O'Connor has drawn attention to the existence of "focal spots," painful places which are found along the affected limb and which persist between the attacks. They possibly correspond with the nodules around the filariae in the course of resorption. It must also be noted that for some time there is a tendency for the lymphangitis to spread out centrifugally around a lymph node (mumu, in Samoa). Lymphangitis is accompanied by a certain degree of *adenopathy.* One can notice the transformation of inflammatory foci into abscesses either in the limbs or in the ganglions (see below). Subacute *funiculitis* and *epididymitis* are frequent. Pain in the region, swelling of the cord and of the epididymis, thickening of the deferent duct, cysts on the epididymis are some of the signs. Sometimes general fever phenomena are observed. The disease may continue toward hydrocele, chylocele, suppurating funiculitis, etc.

Acute or chronic adenitis: They too are very frequent, especially in lymphatic forms, furthermore often associated with the dilatation of the lymphatic vessels of the glands. In India, of 1000 filaria carriers, Cruikshank and Wright have noted 514 inguinal adenopathies, 360 epitrochleans, and 23 auxiliaries.

Abscesses: Attention also has been drawn fairly frequently to these at times mild abscesses, seemingly aseptic, at other times of a more serious kind, extremely septic and even deadly. Septic funiculitis and even retroperitoneal septic lymphangitis has been described. It appears here that the role of the hemolytic streptococci is predominant (Anderson, Grace), possibly facilitated by the lymphatic stasis. However, O'Connor and Hulse consider that the role of the micrococci is of little importance in the majority of abscesses.

Among the manifestations where obstruction is especially evident, *lymphatic varix* and *lymphoscrotum* must be quoted as where these dilatations are most frequently observed. These are ectasias, more or less vesiculous, of the capillaries and the lymphatic vessels, easily resulting in lymphorrhagias which could leave fistulas and wear out the patient by repetition.

Rather similar are varicose dilatations located in the glands themselves (capsular vessels or peripheric sinus) and resulting in *Adenovarix* or *Adenolymphocele.* In the groin and less frequently in the armpits, lumps, flabby to the touch, are observed, enclosed in a cutaneous fold which can be reduced by pressure. This manifestation is different from the firmer adenolymphocele found in the Congo in regions with *O. volvulus.* (See Fig. 76.)

Varicose ruptures can take place in cavities and it is necessary to cite chiliferous ascitis, the most frequent chylocele, of which the nature of the liquid provides the diagnosis: it will be cloudy, rich in cells, or even containing a thick, greasy emulsion. The appearance of real chyliferous overflow leads to the supposition that the obstruction of the lymphatics occurs in the higher ducts: thoracic or intra-abdominal ducts. There sometimes follows a curious and comparatively rare overflow in the urinary ducts: *Chyluria.* This is characterized by the evacuation of urine of milky appearance, sometimes of a pink color due to blood. When at rest, the separation of the urine is made in an upper layer rich in fat, a middle layer containing coagulated albumin and sediment with a little blood and cells (lymphocytes). The lymphatic rupture can take place in the different parts of the urinary ducts and the coagulation of the fibrinogen has resulted in mechanical accidents, ureteral obstruction, etc. Instead of hemochyluria there may be cases of urine filled only with lymph and blood. The evolution of crises in chyluria is very capricious and its influence on the general health varies accordingly. The kidneys are often partly impaired, doubtless because of the lymphatic stases, or even as a result of the obstruction by clots of the excretive ducts. Chyluria is never very frequent. It is apparently not found in Samoa. In Guiana it seems to be discovered in 0.5 to 1.5 per cent of the consultants.

The condition is exceptional in the Congo, but the etiology has not been precisely stated. It must not be forgotten that nonfilarian chylurias exist outside regions where filarial infections are endemic.

It is principally obstruction also, doubtless associated to a certain degree with inflammation, which causes one of the most frequent among filarian manifestations, namely, hydrocele.

Hydrocele: The onset is more or less acute according to the importance of the epididymitis. The active period does not require a special description. As stated above, the fluid may be either serous or lymphochylous. In Samoa, according to Buxton, it is probably an almost universal lesion among the adults. In Puerto Rico, O'Connor and Hulse find it in 13 per cent of the prisoners and 35 per cent of the filaria carriers. In most regions of the Congo, hydrocele seems to appear only in medium frequency, as in Europe. *Elephantiasis arabum* finally is related by most writers with infestation by *Wuchereria bancrofti*. Recognition of this etiology is based on:

1. The geographic correlation: in certain filarian regions there would be between 3–4 per cent and 70 per cent of the population affected by elephantiasis. Yet in other filarian districts (Queensland, Northern Nigeria) it would be totally absent.

2. The frequency in the antecedents of elephantiasis cases of accidents related to filariasis, lymphangitis, etc.

3. The anatomic fact of lymphatic obstruction by *W. bancrofti* and the experimental facts (Drinker) showing how this single obstruction and a consecutive excess of albumin in the lymph suffice to create a pachydermic state.

4. Anatomic findings in the course of operations, showing either hydrocele or epididymo-testicular thickenings, lesions characteristic of filariasis.

5. The role of superadded microbic infection is not well defined and can doubtless be dispensed with.

Diagnosis

The diagnosis of the filariasis of Bancrofti is often purely clinical due to failure in finding microfilariae. These may be absent because the disease is of recent date or because the obstructions of the lymphatics hinder the access of embryos into the blood. Moreover, obstruction seems to result in the death of adults.

Eosinophilia may be of a certain indicative value. Research should be made into the more or less typical adenopathies, hydrocele, the focal spots of O'Conner. Cutaneous tests or the deviation of the complement may prove useful. Examination of the blood will be made both by day and by night.

Treatment

Neostibosan in large doses has recently been recommended (Culbertson and colleagues). Other writers who believe in the provocative role played by the streptococci make use of sulfonamides, besides associating local therapeutics with it.

Lately, Hetrazan (1-diethyl-carbamyl-4-methyl piperazine) has been successfully used in Puerto Rico (Santiago-Stevenson, Oliver Gonzalez and Hewitt, 1947). The drug was given orally (0.5 to 2 mg./Kg. of body weight, three times a day from three to twenty-two days). The treatment reduces the microfilarial count to zero. The low mammalian toxicity of Hetrazan makes the use of this drug conceivable for the prophylaxis of *W. bancrofti.* Its action on other filariases is so far not known.

Abscesses, hydroceles, adenitis, lymphangitis may necessitate minor or major surgical intervention.

The treatment of elephantiasis will be examined further on.

Prophylaxis

Prophylaxis consists essentially in the destruction of mosquitoes (see under Malaria and Yellow Fever) and the protection from their bite by house screening and the use of mosquito nets at night. This should be compulsory for every carrier of microfilariae.

Culex fatigans, the most important and prevalent vector, is highly ornithophilic. The keeping of fowls should therefore be encouraged in endemic areas in order to distract mosquitoes from biting man.

(F) WUCHERERIA MALAYI

History: The microfilariae were first seen in Celebes by Lichtenstein and described by Brug as a new species (1927). The adults were found only in 1940.

Geographic Distribution: *W. malayi* is found in Indonesia, Indo-China, China, Assam, Ceylon, often together with *W. bancrofti*.

Etiology: *W. malayi* closely resembles *W. bancrofti*. The microfilariae are easily distinguished by two minute nuclei in the tip of the tail, one of which is strictly terminal (see chart of differentiation, page 351 and fig. 84). The microfilariae show little periodicity with a maximum number at 4 A.M.

Transmission occurs by several *Mansonioides* and *Anopheles* mosquitoes.

Symptomatology: Elephantiasis is commonly found among infected people, and, according to Brug and others, more on the limbs than on the genitals.

Prophylaxis is essentially the same as for *W. bancrofti*. The cleaning of swamp and ponds of Pistia plants has been very successful in the elimination of Mansonioides. The larvae and pupae of these mosquitoes develop under water, obtaining air by piercing the stems of aquatic plants, especially of Pistia.

(G) ONCHOCERCA VOLVULUS

History

Onchocerca volvulus was first seen and named by Leuckart (1893) in the nodules of two natives of the Gold Coast. Brumpt (1904) found 15 cases along the Uele River in the Congo. In 1915 Robles found a nodule on the head of a child in Guatemala and in 1916 described the Filaria. He pointed out that the nodules on the head were associated with ocular disturbances and that a definite erysipelas, called "erysipela de la costa" was also related with the condition. Brumpt in 1919, on clinical ground alone, separated the American species under the name of *Onchocerca caecutiens*, with the assumption that whereas *O. volvulus* had been related to elephantiasis of the genitals in Central Africa (Ouzilleau, 1913, Dubois 1915–1917) this disease was never encountered in Central America. The nodules of *O. caecutiens* were mostly located on the head causing a blinding disease whereas the nodules of *O. volvulus* were found mainly on the lower part of the body. Slight morphologic differences were also given between the males of both species, but Fülleborn (1924) and Sandground (1933) showed that these differences were within the variation range of *O. volvulus* itself. By this time a Belgian oculist, Hissette (1932) discovered the ocular Onchocerciasis in Congo, proving that even on clinical ground there remained no reason for separating both species. This important discovery was confirmed in the Congo by Strong, Bequaert, and Sandground who had the widest experience of both American and African conditions. The disease appears thus as the same on both continents and is now generally attributed to *Onchocerca volvulus*.

In 1926 Blacklock showed in Sierra Leone that *Simulium damnosum* is capable of transmitting the infection. It was only in 1946 that Wanson and Henrard in the Congo gave definite proof of this, after succeeding in infecting laboratory bred *Simulium damnosum*, on *Onchocerca* carriers.

Geographic Distribution

Onchocerciasis is known in Africa, from Sierra Leone, Liberia, the Sudan on the north and the Congo, Rhodesia, and Nyassaland to the South. The rate of infections varies in different parts from 45 per cent (Sierra Leone) to over 75 per cent (in certain districts of the Congo).

The disease in Africa is rather patchy, but seems to spread. We have seen in recent years an extension of Onchocerciasis in certain parts of the Congo, for instance in Leopoldville. In Central America Onchocerciasis is endemic in certain regions of Guatemala and Mexico (provinces of Chiapas and Oaxaca, at altitudes from 700 to 1500 meters, regions of coffee plantations).

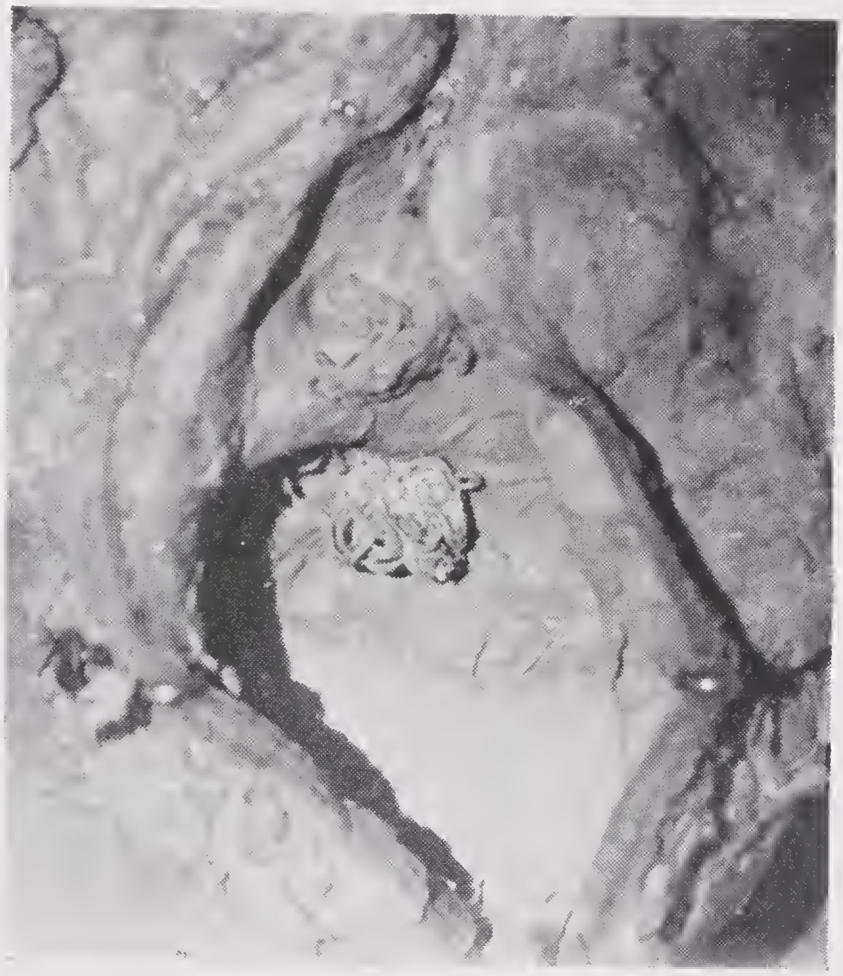

FIG. 73a. ONCHOCERCA VOLVULUS INSIDE A NODULE

Morphology

The adult worms are found in nodules situated generally between superficial bones and the skin. They may also occur free in connective tissue. In two autopsies upon Congo natives showing Onchocerca nodules, free adult female parasites were discovered between the fibers of the fascia lata and in the region of the trochanter (van den Berghe 1936). Human infections are known in which microfilariae are present and where nodules cannot be recognized. Some Onchocerca species, morphologically identical with *O. volvulus,* and found in horses, buffaloes and antelopes are not enclosed within nodules but are found in tendons, especially in the ligamentum nuchae. It seems, however, that in human cases the irritation exerted by the parasite is such that sooner or later a definite nodule surrounds the adult Onchocerca. These worms possess rings of the cuticle, reinforced by spiral thickening. The male measures approximately 20 to 30 mm. in length by 0.12 to 0.20 mm. in breadth. The females are so interlaced within tissue that they are very difficult to secure in toto. They measure 300 to 500 mm. in length and 0.25 to 0.40 in breadth. The uterus is filled with ova or embryos. *O. volvulus* is viviparous.

The microfilariae are found almost exclusively in the connective tissue of the dermis, conjunctiva, and other tissues of the eye. They have been reported in lymphatic glands and in some instances in the deeper tissues and viscera (Rodhain). They vary greatly in size, from 200 to 300 μ in length and from 7 to 8 μ in width. They possess no sheath and are actively motile. Their appearance in the blood is purely accidental and due to the puncture through the dermis with the needle.

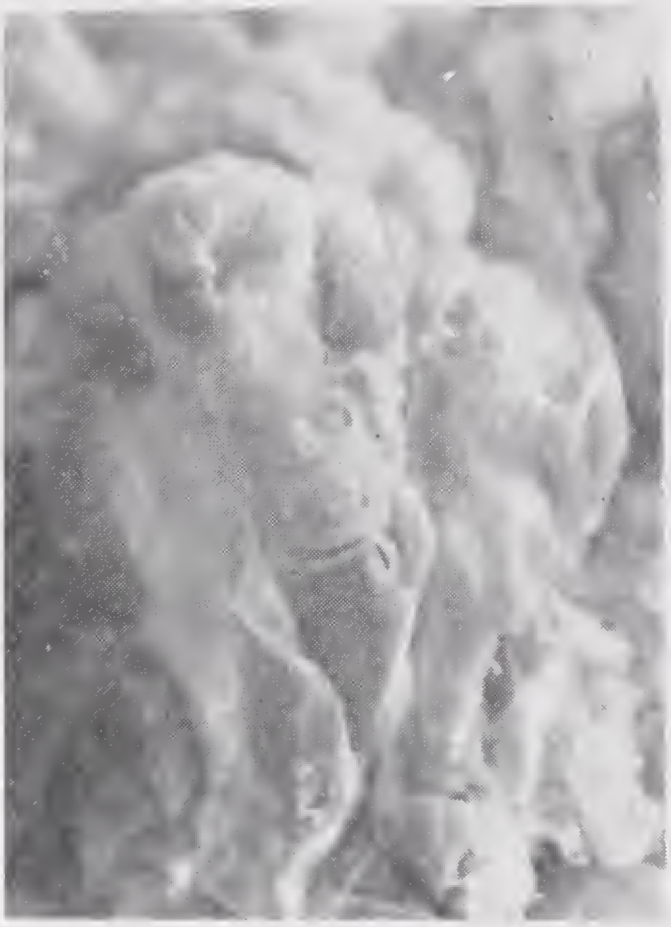

FIG. 73b. ONCHOCERCA VOLVULUS OUTSIDE A NODULE

Free in the connective tissue. Found exceptionally in the Congo (L. van den Berghe)

Transmission

O. volvulus is transmitted by several species of a small black fly of the genus *Simulium: S. damnosum* and *S. neavei* in Africa, *S. avidum* (*metallicum*), *S. ochraceum* and *S. mooseri* (*callidum*) in Guatemala, *S. mooseri* in Mexico. Simulium flies breed in swiftly flowing rivers or brooks. The larvae pupae are attached to stones, logs, leaves, or stems of plants immersed in well aerated water. The flies sometimes range considerable distances (up to 70 kilometers from their breeding places according to Gibbins in Uganda). In Africa the vectors breed in low altitudes and the disease is very common below 500 meters. In Guatemala and Mexico, on the contrary, onchocerciasis occurs endemically only between 700 and 1500 meters. The disease in the Western Hemisphere is especially related with coffee plantations in mountainous regions, because the vectors there do not breed below some 700 meters. In the coffee districts of Guatemala and Mexico, from 30 to 100 per cent of the individuals are infected. The Simulium are day biting flies (between 8 A.M. to 6 P.M.). Only the female fly bites and transmits the disease.

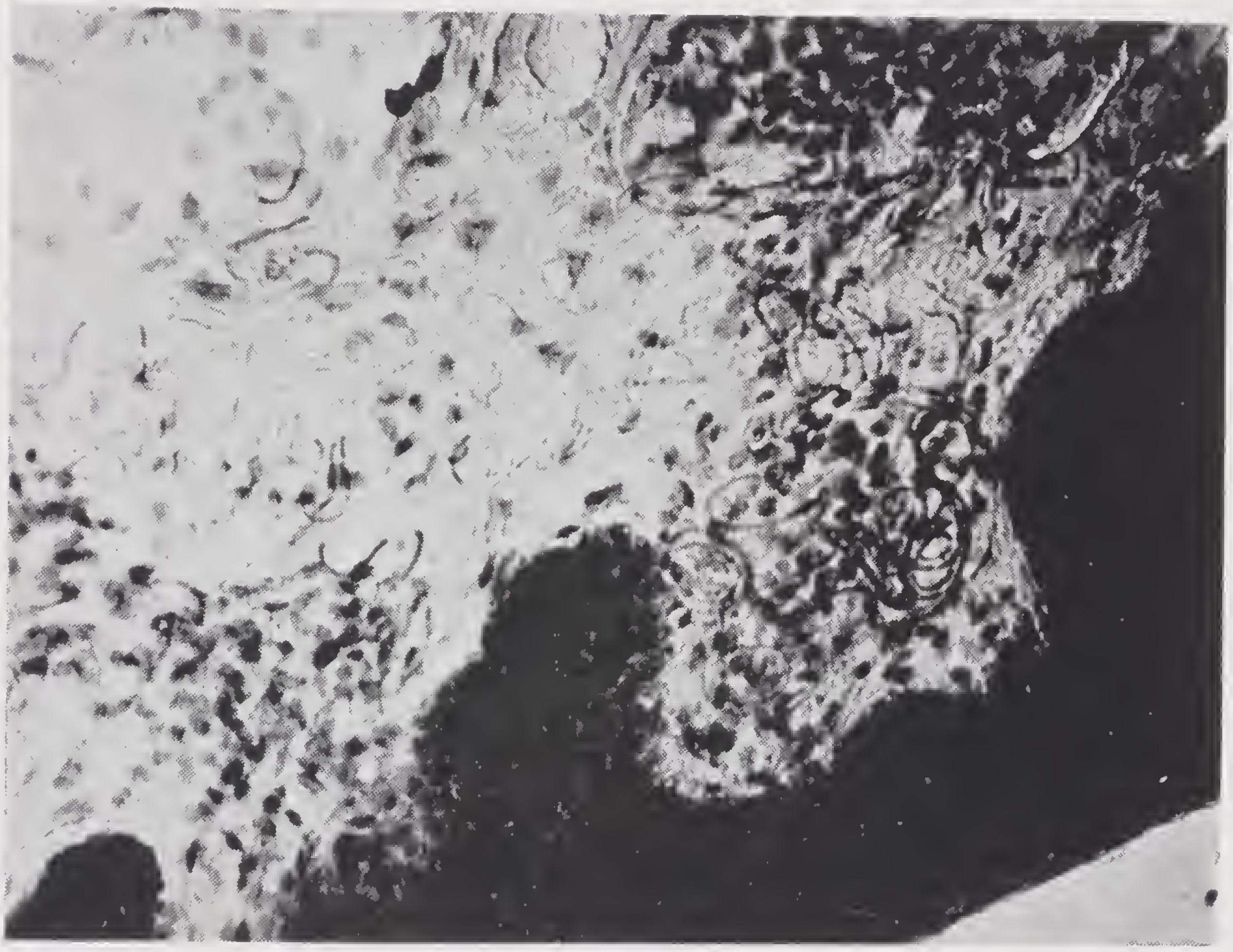

FIG. 74. SECTION OF THE SKIN WITH DERMIC MICROFILARIAE. UELE, CONGO
Coll. Tropical Institute, Antwerp

The microfilariae, after being ingested by the fly, migrate from the gut to the thoracic muscles, and become the "sausage-forms." After several moults, the parasite assumes a long and slender form and passes to the head and proboscis. The development is completed after six to seven days. Only a few larvae (from 1 to 10) are found in each infected fly. It seems that the Simulium cannot survive a heavier infection.

The rate of infection among the flies varies from 5 per cent in Guatemala to 9 per cent in certain regions of the Congo (near Leopoldville, in the Uele) and to 33 per cent in other parts of the Congo (Lusambo). The Onchocerca develop slowly in the human host (several months probably).

Pathology

O. volvulus stirs up marked organic reactions in its larval as well as adult states. The adult is very frequently, if not always, surrounded by a sclerous nodule. The term cyst is not quite exact but is in common usage. The reaction which produces the nodule is very sluggish. In the young nodules there is a granuloma resembling the granulomas of foreign bodies. Epithelioid cells, often showing lipoidic degeneration of the cytoplasm ("lipophages"), lymphocytes, plasmocytes, and fibrocytes, compose the young nodules.

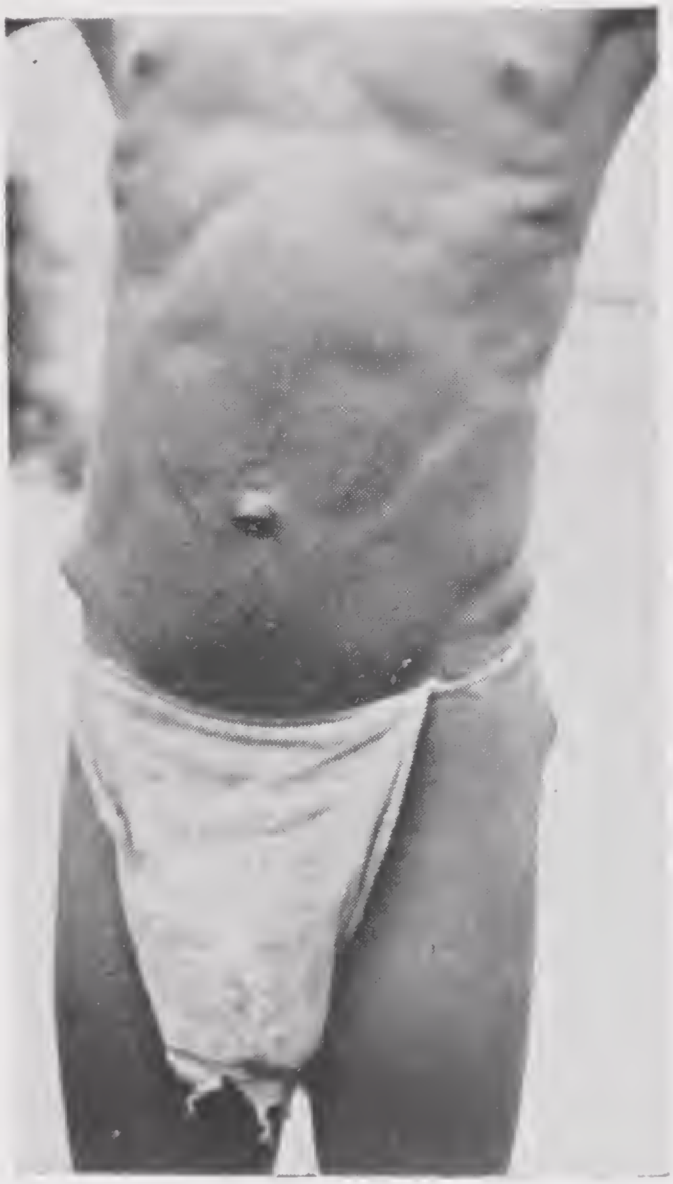

FIG. 75. ONCHOCERCA VOLVULUS NODULES
Ileum trochanter, common sights in Africa (L. van den Berghe)

Giant cells are seen around the dead worms in the course of resorption. Old nodules have a more marked fibrosis and cavities of necrotic origin containing an orange colored liquid and very frequently an exudation of a purulent nature. In certain cases pus fills the dilated nodule and is found to be rich in crystals of cholesterol. The adult worms have died off, causing a purulent change.

Microfilariae cause a chronic inflammation in the skin, in the cornea and the lymphatic glands characterized in the former organs by plasmocyte and lymphocyte infiltration, with a slight vascular neoformation. Do the microfilariae act as irritant bodies or is a previous sensitization to the filarial antigen necessary? This question has not been solved. In the same degree, within the lymph nodes Rodhain has found sclerosis, plasmocyte or eosinophile infiltration, and a certain lymphatic stasis. He attributes the whole of these lesions to the parasite.

Symptomatology

The filarial nodules appear as small, firm, hard tumors adhering incompletely to the skin, and in most cases, sluggish. Their size varies from 3–4 mm. to 3–4 cm., the average size being 1.5 cm. They hardly ever ulcerate although their contents are sometimes of a purulent nature.

In certain regions, 80 to 90 per cent of the adults may show nodules. The number varies in an individual between 1 and 3 (frequent cases) or from 20 to 30, up to 100 and more. In this case the nodules are very small. Their favorite site is between the skin and a superficial bone surface: the ilium, the sacrum, trochanter (localizations predominating in Africa), the ribs, scalp (localization predominating in Central America). They are found especially in adults, although they have been found under the age of one year (Strong) and even at the age of three months (Robles).

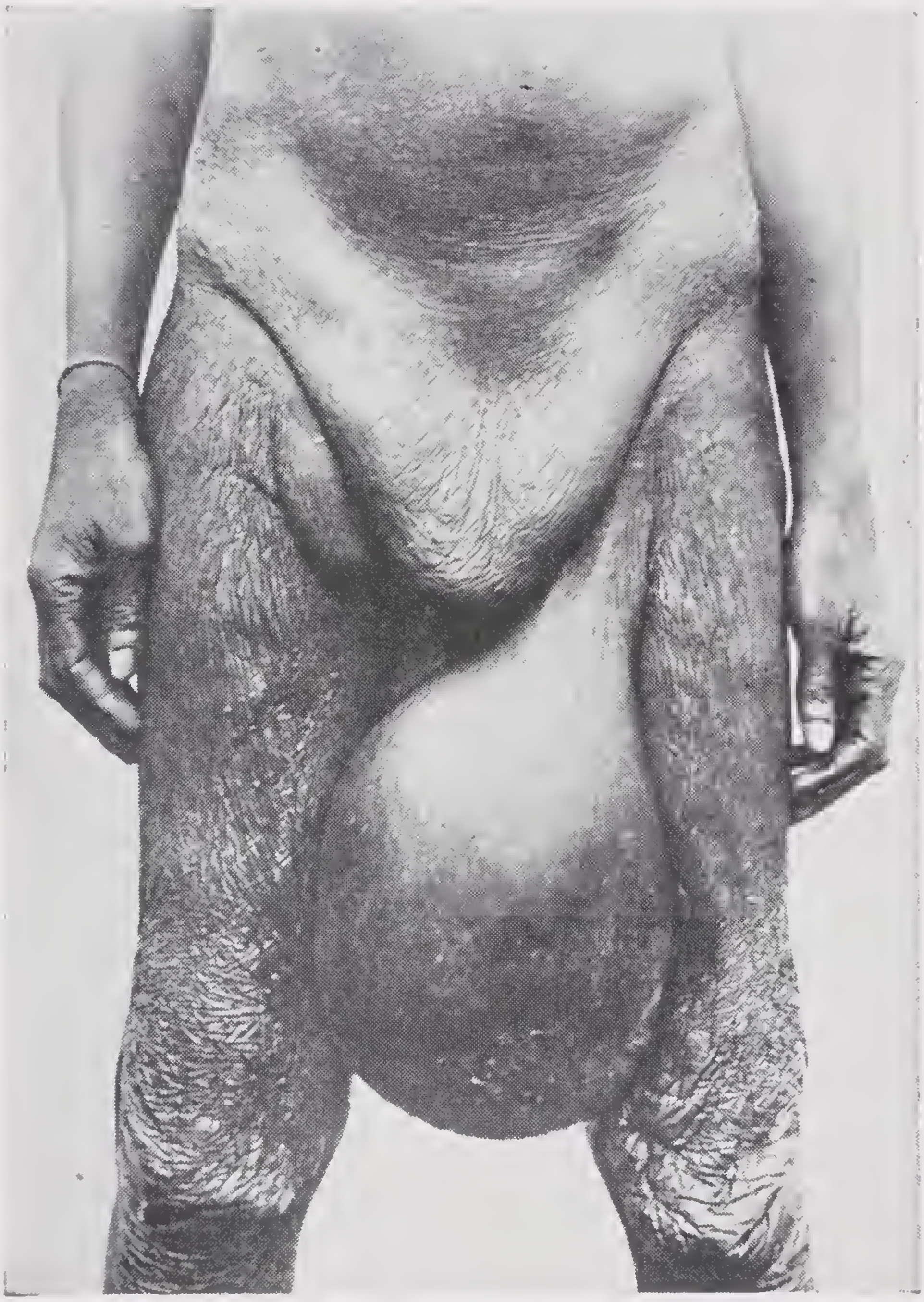

FIG. 76. ADENOLYMPHOCELE WITH XERODERMIA OF OUZILLEAU. UELE, CONGO
Phot. D'Hooghe, Tropical Institute, Antwerp

Adenopathy: Nodule carriers frequently show an indolent adenopathy of the inguinal and cervical glands which perhaps may be attributed to filariae. In certain cases what has been described under the name of adenolymphocele appears: a pendulous inguinal tumor made up of a cutaneous fold enclosing various hypertrophied and sclerous glands; its size may be considerable. Here again the relation between the clinical syndrome and the parasite is rather obscure. This type of tumefaction seems harder than the adenovarix seen in *W. bancrofti* infections.

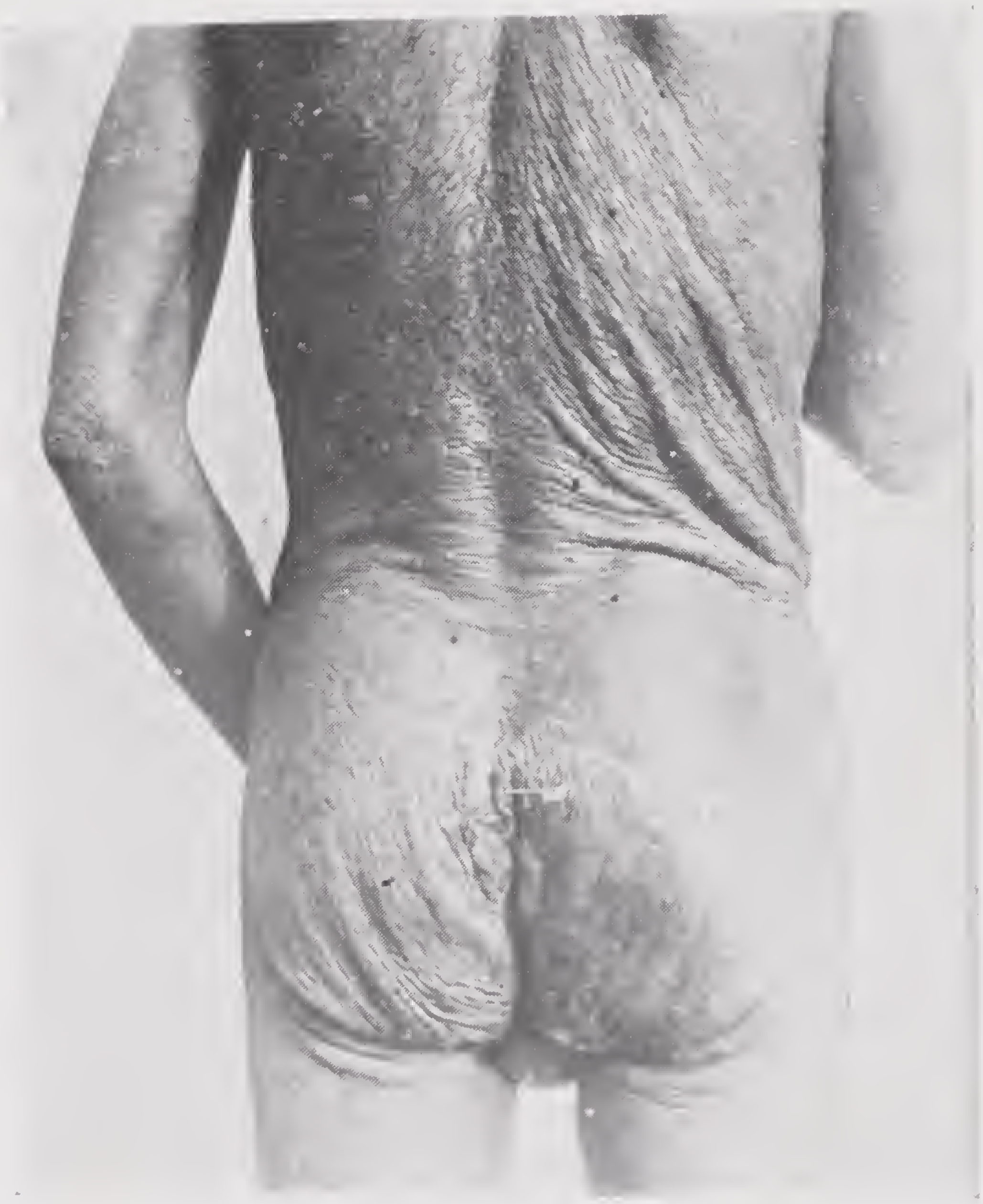

FIG. 77. CUTANEOUS ONCHOCERCIASIS IN THE UELE, CONGO
Phot. D'Hooghe, Tropical Institute, Antwerp

Filarial prurigo: This affection, whose advanced stage Ouzilleau has described under the name of "Xerodermia," has been distinguished from other prurigos by two French dermatologists, Montpellier and Lacroix, who studied black riflemen in Africa. This syndrome is rightly attributed to *O. volvulus* because of its frequency in infected patients and in the geographic localities of this filaria. In Europeans in particular, infection by *O. volvulus* is accompanied very frequently by prurigo (at least 50 per cent). Moreover, we know the regularity of the dermotropism of the microfilariae of this species and the frequency of the histologic inflammatory reaction along vascular nervous dermic plexuses. Not all the filariae carriers show these cutaneous signs and it is possible that a favorable ground and a sensitization to the filarial allergene may be the cause. Gibbons and Loewenthal at one time held the reaction to the bites of Simulium responsible, but in general this does not appear to be true for Europeans, at least when they have returned to their native country. Moreover, Loewenthal has given up this theory.

The fundamental symptom of filarial itch is prurigo, developing by irregular attacks and accompanied by a papulous and sometimes pustular reaction. Ultimately, lichenization becomes important and may be accompanied by pachydermia.

Finally, sclerosis and atrophy of the derma cause a thin senile skin, covered with a shining epidermis with diamond shaped markings like lizard skin (Ouzilleau's Xerodermia). Lesions prevail on the back, the buttocks, the outside surface of the limbs, sparing the face, the extremities and the genitals. The cutaneous signs seem rare, even absent in Central America. They have, however, been observed in Europeans, and recently described in natives under a form which closely resembles the African one (Goldman and Ortiz, 1946).

Elephantiasis: Since Ouzilleau (1913), Dubois (1916), the hypothesis which attributes elephantiasis to *O. volvulus* has been widely discussed many times without being solved. We shall study it further with elephantiasis.

Ocular Onchocerciasis

In 1916 Robles and later Luna and Calderon described the disease in Guatemala, while Ochoterena, Torroella, and Silva extend this knowledge to certain regions of Mexico. The symptoms begin late and progressively 5 or 6 years after the first appearance of nodules: photophobia, abnormal conjunctival sensation, and slow evolution of lesions in the cornea and uvea.

These ocular complications are frequent (15 to 20 per cent in American carriers) and this probably because of the predominance in certain countries of the cephalic localization of the worms with an abundance of microfilariae in the skin of the face and the neighboring ocular membranes.

Ocular onchocerciasis was observed in 1932 by Hissette in the Sankuru (Congo). It attains great frequency there: for example, 211 adults of a village had nodules 199 times and ocular lesions 159 times, of which 57 were amaurotic. Since then such phenomena have been found in various parts of Africa, including the Congo, but never in such proportions. D'Hooghe notes 2 per cent of ocular lesions and 0.5 per cent of blindness (80 per cent of nodules). The frequency of ocular troubles in Sankuru may be in relation with the abundance of cephalic nodules as in Guatemala, and contrary to Uele.

Hissette describes the affection as being a torpid iridocyclitis. However, the filarial invasion is probably by continuity of skin, conjunctiva, cornea, and we may wonder whether this systematization is not excessive. Hissette considers that the first clear objective symptom is the change of the pigmented edge which borders the pupil, especially in the lower hemicycle and a deep perikeratic injection.

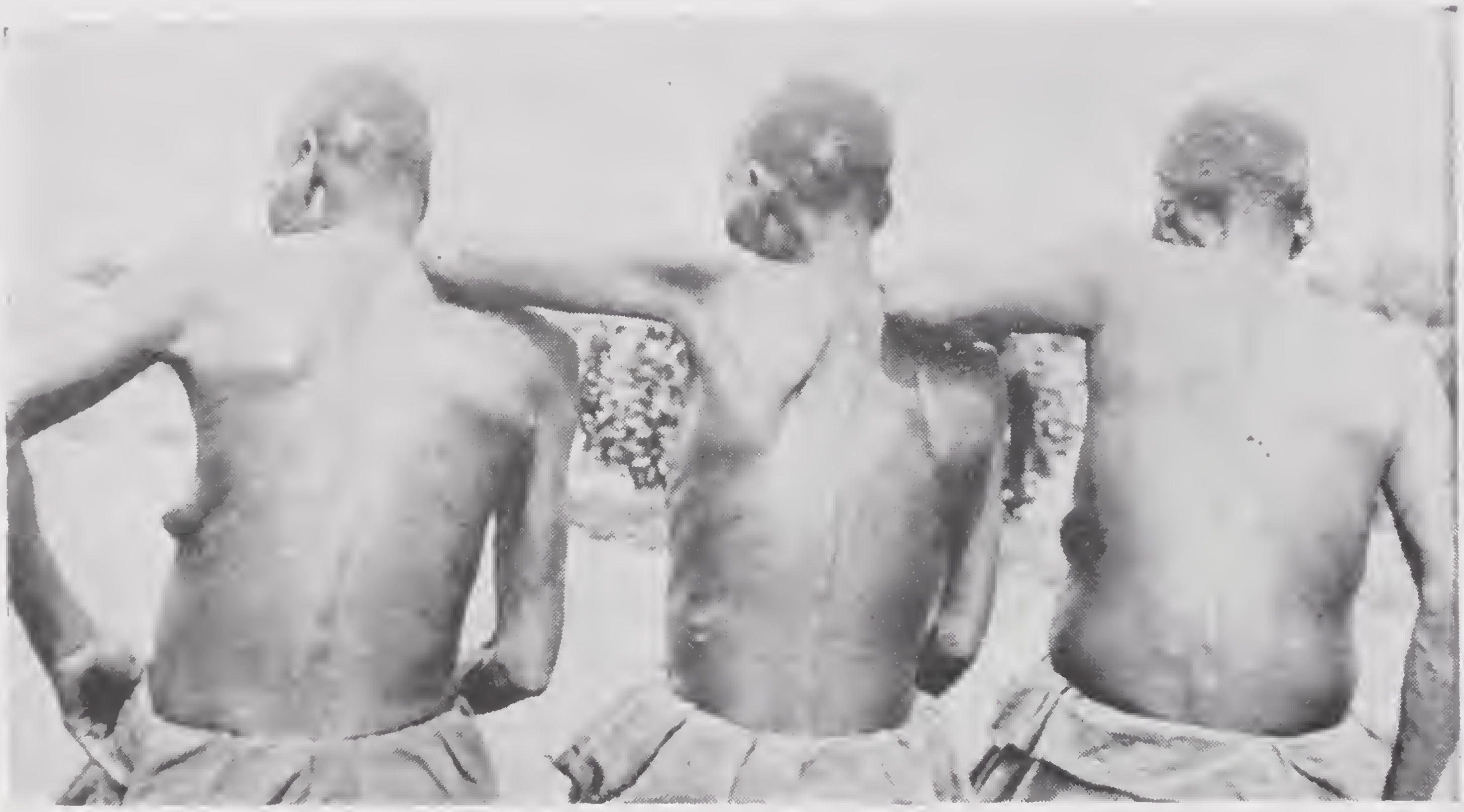

FIG. 78. OCULAR ONCHOCERCIASIS
Three cases from the Uele with nodules on the head and trunk, common sight in Central America, rare in Africa (L. van den Berghe)

We also note very early a swelling of the eye lids, conjunctival redness and punctuation of the cornea due to small exudative foci. Keratitis is then declared, a horizontal pannus appears, and signs of uveitis (change of the pupil, perikeratic redness, synechias) and chronic chorioretinitis are manifested with finally, sometimes, an atrophy of the eyeball.

Subjective signs are rather vague: abnormal ocular sensations, photophobia, decline of visional sharpness. African natives sometimes declare they see serpents of fire, which we suppose correspond to the entoptic appearance of the larvae.

Prognosis

Onchocerciasis appears as a serious affection because of the frequency of cutaneous troubles and especially ocular disturbances. Hissette considers it the most important cause of amblyopia and of amaurosis in Central Africa.

Diagnosis

Clinically, confusion is possible between filarial nodules and small cutaneous tumors (fibromes, juxta-articular nodosities). The latter are harder, more adherent to the skin, and more symmetrical. Excision or puncture is the simplest means of diagnosis. Ordinarily puncture brings out fragments of adult worms, eggs, and easily recognizable microfilariae (see below: microscopic diagnosis).

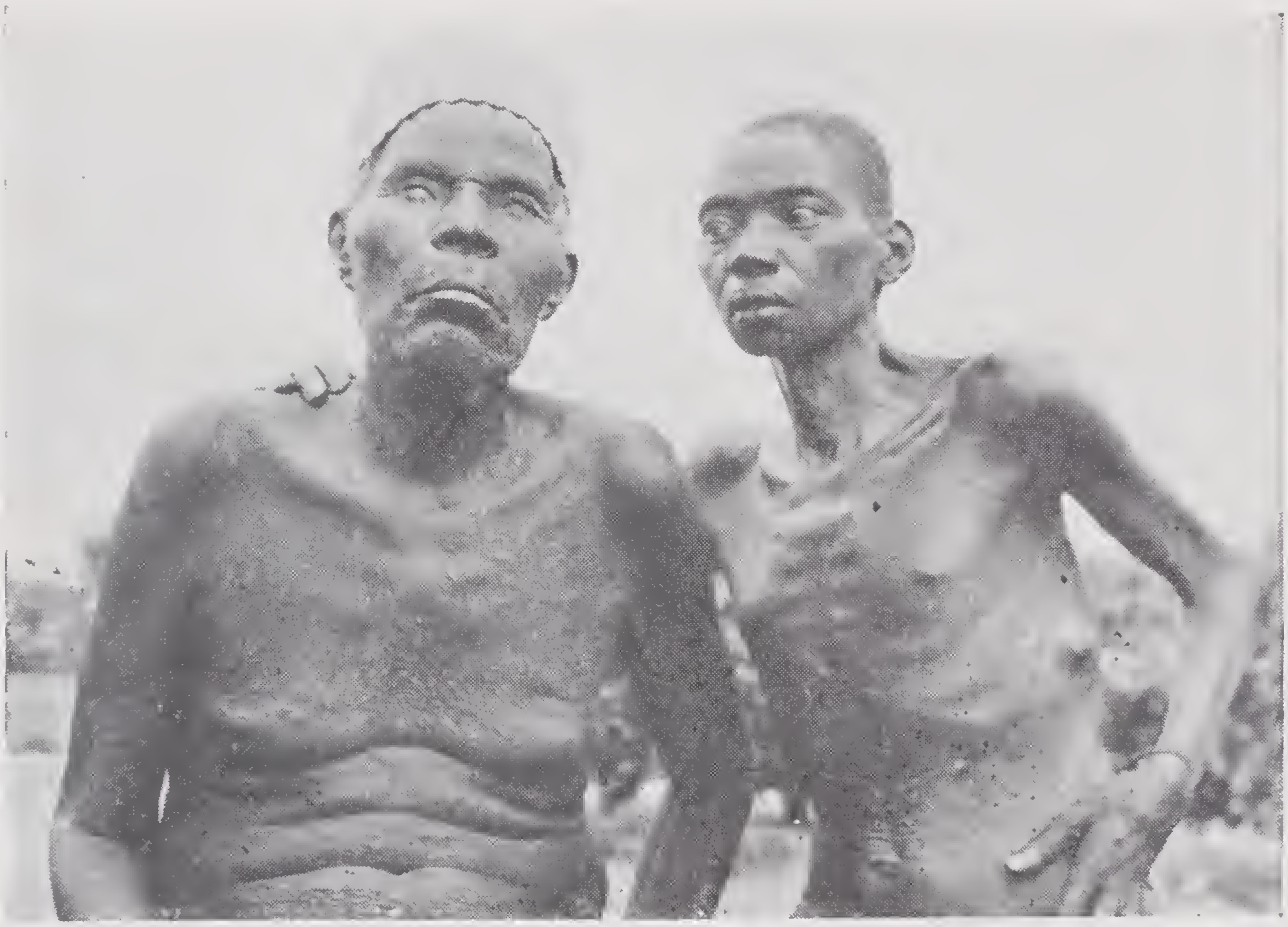

FIG. 79. OCULAR ONCHOCERCIASIS
Two cases with blindness from the Uele (L. van den Berghe)

Adenopathy is of uncertain clinical diagnosis and even its attribution to filariasis is not above all discussion.

The prurigo must be distinguished from various parasitic and other prurigos. Sarcoptic itch is easily recognized: varying distribution (wrists, fingers, penis, etc.), wrinkles and vesicles, marked tendency to pyodermitis, action of the treatment. The finding of Sarcoptes will settle the diagnosis. Care must be taken, for it is evident that the two parasites may be present. The same observation is true for ocular manifestations which may be confused with ophthalmia from other causes.

All this finally brings us back to the parasitic diagnosis. The adult worm must be looked for by careful palpation of all the cutaneous surface and excision or puncture of every nodule suspected. If we wish to have only an idea of frequence in the palpation it is sufficient to palpate the favored areas (iliac, sacrum, ribs, trochanters, the scalp). We must puncture a sufficient proportion of nodules in order to affirm the correctness of the diagnosis.

The microfilariae may be found in the lymph nodes, but rarely in number and sometimes the identification is rather uncertain.

A more certain procedure is to make the research in the derma. Several procedures are used: (1) by taking a cutaneous fragment and placing it in 2 to 3 drops of physiologic water in which the larvae are found; (2) excision with a razor blade of a fine slice of the papillary derma which we examine under the microscope between slide and cover slip; (3) slight scarification covered by a drop of saline spread on a smear after two or three minutes. (4) The best method consists in a scarification of the derma, then waiting until a little bloody serosity appears instead of blood and making a thick drop. This fluid contains dermic filariae (*O. volvulus* and *A. streptocerca*) and also eventually sanguicolous microfilariae (*loa*, *perstans*, *bancrofti*). It is possible to distinguish them after staining (see charts, pages 350 and 351).

The microfilariae may also be sought in the tissue of the conjunctiva after excision with curved scissors of a minute scrap (head of a pin) which must be examined immediately in a drop of saline.

Identification on a skin section is always uncertain for lack of sufficient and characteristic filarial fragments. Thick sections by congelation are often more favorable.

Finally, it is possible to observe the microfilariae in the humor aquosa or in the cornea, thanks to the corneal microscope. This can be most instructive.

Serologic methods, deviation of the complement and cutaneous test have only a group significance.

Treatment

The first American observers reported cures of ocular troubles by excision of nodules but later observers have not confirmed these favorable results or at any rate have shown only passing improvement. The natives of Guatemala, however, are anxious to see the nodules extirpated and if these are not numerous this intervention is certainly useful.

An intra-nodular injection of Rivanol, 1 per cent, is much more expeditious. Hissette only punctures the nodule in several directions with a thick needle. This brings final atrophy.

As a general treatment, emetic, fouadine, neostibosan, etc., have been tried without appreciable results.

Murgatroyd advises the desensitization by injection of extract and it seems to us that this is worth trying.

Van Hoof and colleagues have recently (1947) treated onchocerciasis with Bayer 205 and have obtained the disappearance of dermic microfilariae as well as the death and resorption of adults contained in the nodules. They give repeated doses of 1 Gm. to 1.50 Gm. twice a week. When the full cumulative dose of 5 Gm. has been reached, the death of the worms produces a violent reaction with fever and articular pains, exfoliation at the level of the dermic lesions and inflammatory reactions in the ocular lesions. This reaction is sometimes dangerous. The total dose of 8 Gm. in injections given with care at sufficient intervals would lessen the reactional phenomena and cause all the *O. volvulus* to disappear.

Prophylaxis

The biology of the Simulium is such that the individual as well as the social prophylaxis of onchocerciasis is one of the most difficult problems to solve.

1. The eradication of Simulium seemed an almost futile attempt until the recent encouraging experiments with immersed stones made of cement and DDT and placed upstream. It appears that an efficient concentration of the larvicide is thus provided in the running water. Garnham, in Uganda (1947), in using the drip method upstream, obtained total eradication of Simuliums.
2. Infected people, the only known reservoir, should be treated. The removal of nodules has been widely practiced but can only reduce the severity of the infection, as many nodules are too small to be located and as some adults may be unenclosed in nodules. The use of Bayer 205, as advocated by Van Hoof and colleagues, appears to us as too toxic to be the answer to this problem.
3. The protection of man against day biting flies can be insured by appropriate clothing and the use of the already mentioned repellents.

12. ELEPHANTIASIS

Two, or even three, types may be distinguished:

1. *Elephantiasis nostras:* Sporadic cases are observed in all tropical countries; their basis is a glandular obstruction due to various pathologic causes: repeated lymphangitis of varicose and other ulcers, cutaneous tuberculosis, cancer, etc. At other times this elephantiasis is cryptogenic: Castellani has described special microbes whose role has not been established.
2. *Elephantiasis arabum (Arabian elephantiasis):* It is endemic in areas where *W. bancrofti* exists and sometimes follows manifestations of filaria,

for instance in repeated lymphangitis; sometimes, on the contrary, it appears in an insidious manner. According to O'Connor and Hulse the latter eventuality is most frequent in Puerto Rico, where on 301 cases the writers had 240 "primary" cases and only 59 "secondary," that is, following lymphangitis.

3. *Congolese elephantiasis:* One of the writers (A. Dubois) has felt for some time that this form should be distinguished from Arabian elephantiasis. In Central Africa, *W. bancrofti* seems absent in many places where elephantiasis exists. No doubt this observation may be due to insufficient research and as we have stated above, the recent discovery (Fain) of *W. bancrofti* in certain places of the Congo weakens this parasitologic argument. However, it seems certain that in various regions of the Congo where elephantiasis (particularly the scrotal) is common, not only are *W. bancrofti* absent, but also all the pathologic complex (repeated lymphangitis, hydroceles in great frequence, lymphatic varicoses, etc.) which has been attributed to it. Besides, one of the writers (A. Dubois) having operated upon 60 to 70 cases of scrotal elephantiasis, noted the absence of lesions of the testicles and spermatic ducts. The parasitology, clinical medicine and pathologic anatomy tend to separate the

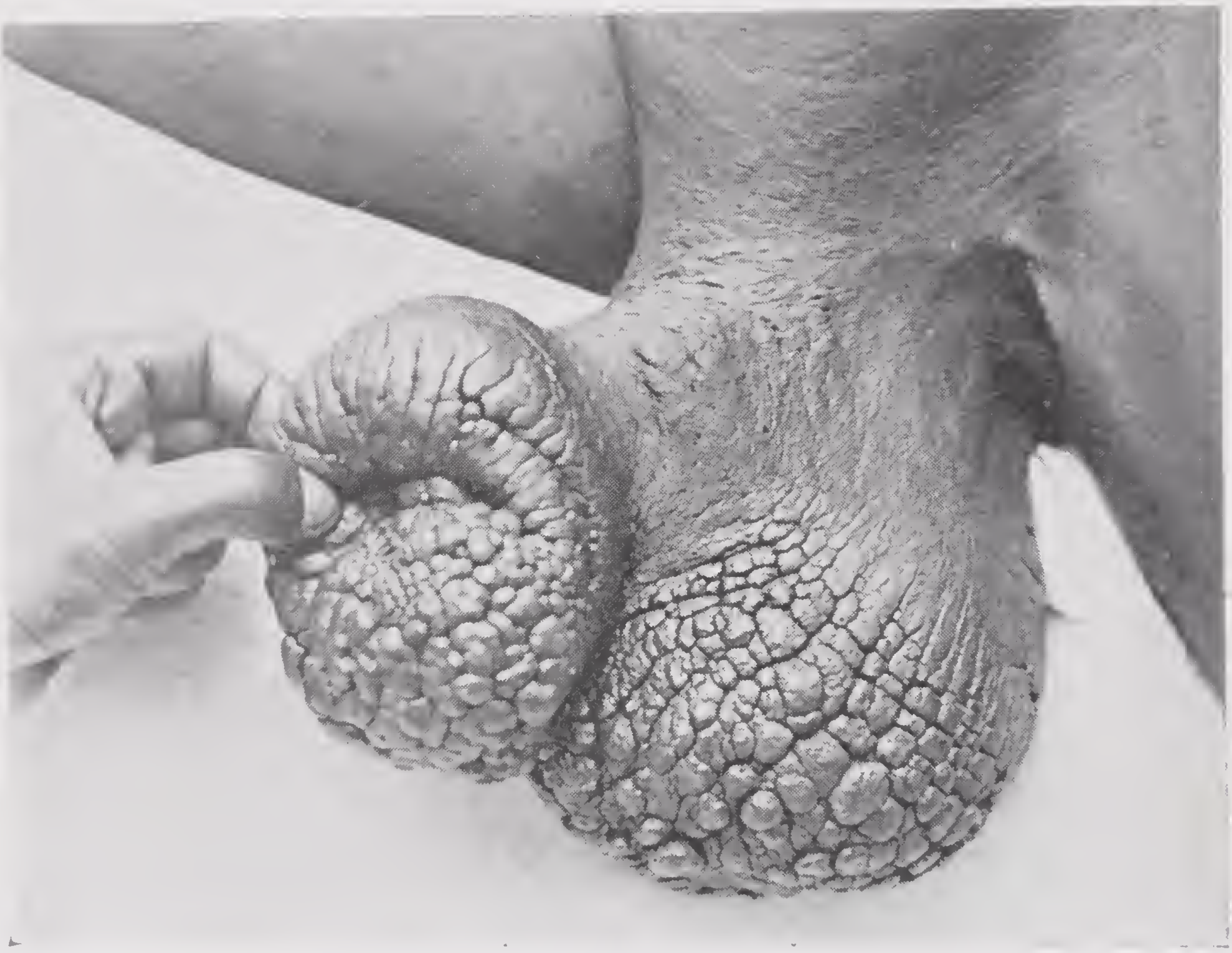

FIG. 80. GENITAL ELEPHANTIASIS
Early stage from the Congo (coll. Tropical Institute, Antwerp)

Congolese disease from the more widely spread form due to *W. bancrofti.*

As stated above, the attribution of Congolese elephantiasis to *O. volvulus* attempted from 1913 by Ouzilleau, supported in 1915–1917 by Dubois, has never been established in a manner to exclude all discussion. In this case even more than with *W. bancrofti*, evidence is uncertain: we must particularly note the fact that there are countries where *O. volvulus* is frequent and where elephantiasis is of no special importance (Guatemala, and the Kasaï region in the Congo). In Central America, however, the "erysypelas de la costa" has been related to *O. volvulus*. Chronic thickening of the skin may result from this condition which has been compared by certain authors to elephantiasis. One should not expect mechanically a very pronounced elephantiasis on the upper parts of the body (face).

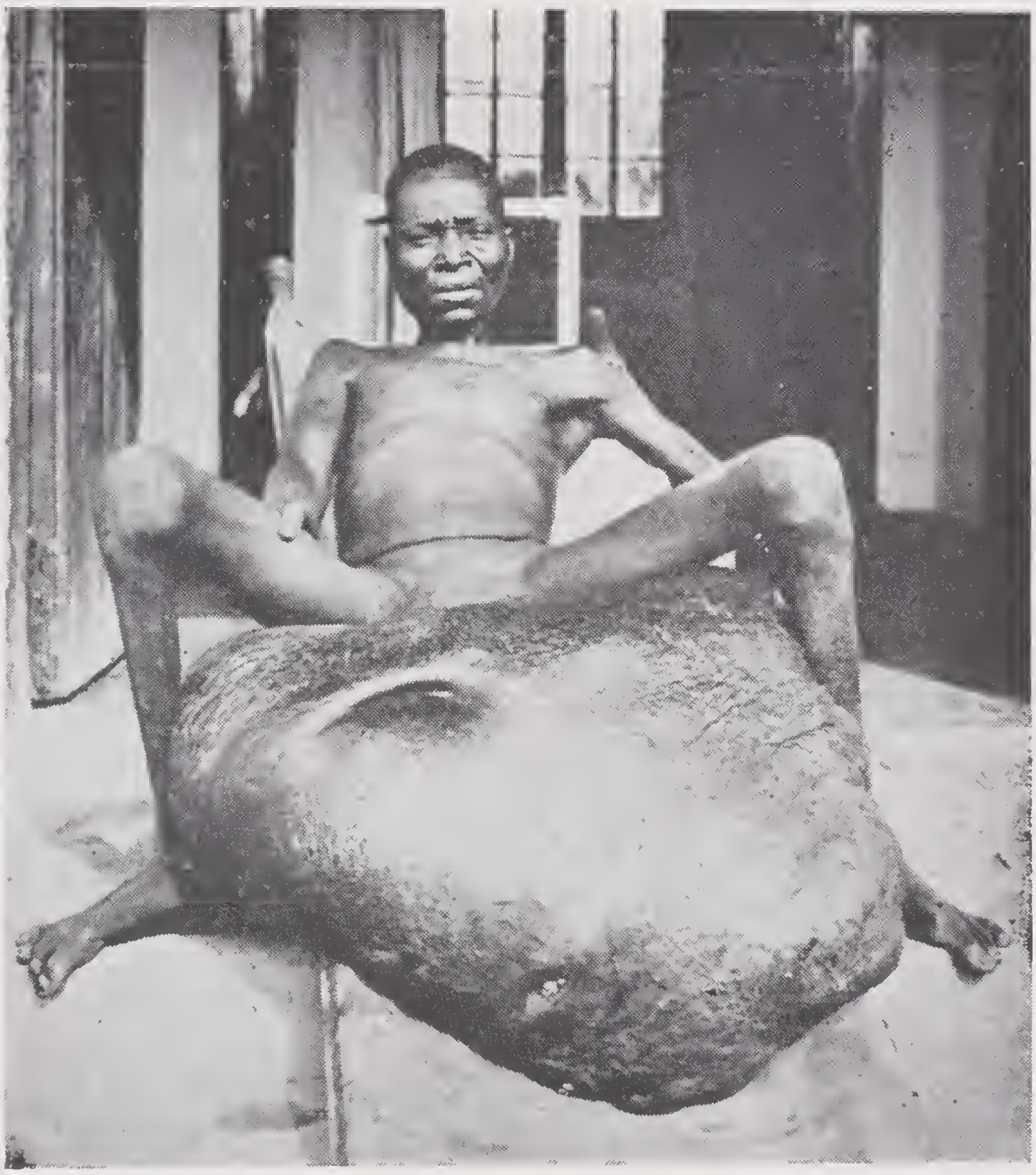

FIG. 81. GENITAL ELEPHANTIASIS
Onchocerca region of the Congo (coll. Tropical Institute, Antwerp)

The recent discovery of *Acanthocheilonema streptocerca* in Central Africa (Dubois, Peel, and Chardome), with the dermic localization of its microfilariae, renders the problem even more complicated.

At any rate, the pathogenic mechanism producing elephantiasis is more obscure for *O. volvulus* than for *W. bancrofti*. In the latter case the obstructive lesions of the lymphatic glands explain the stasis of the lymphatics sufficiently, while in *O. volvulus* the glandular lesions are of a more discrete character (Rodhain).

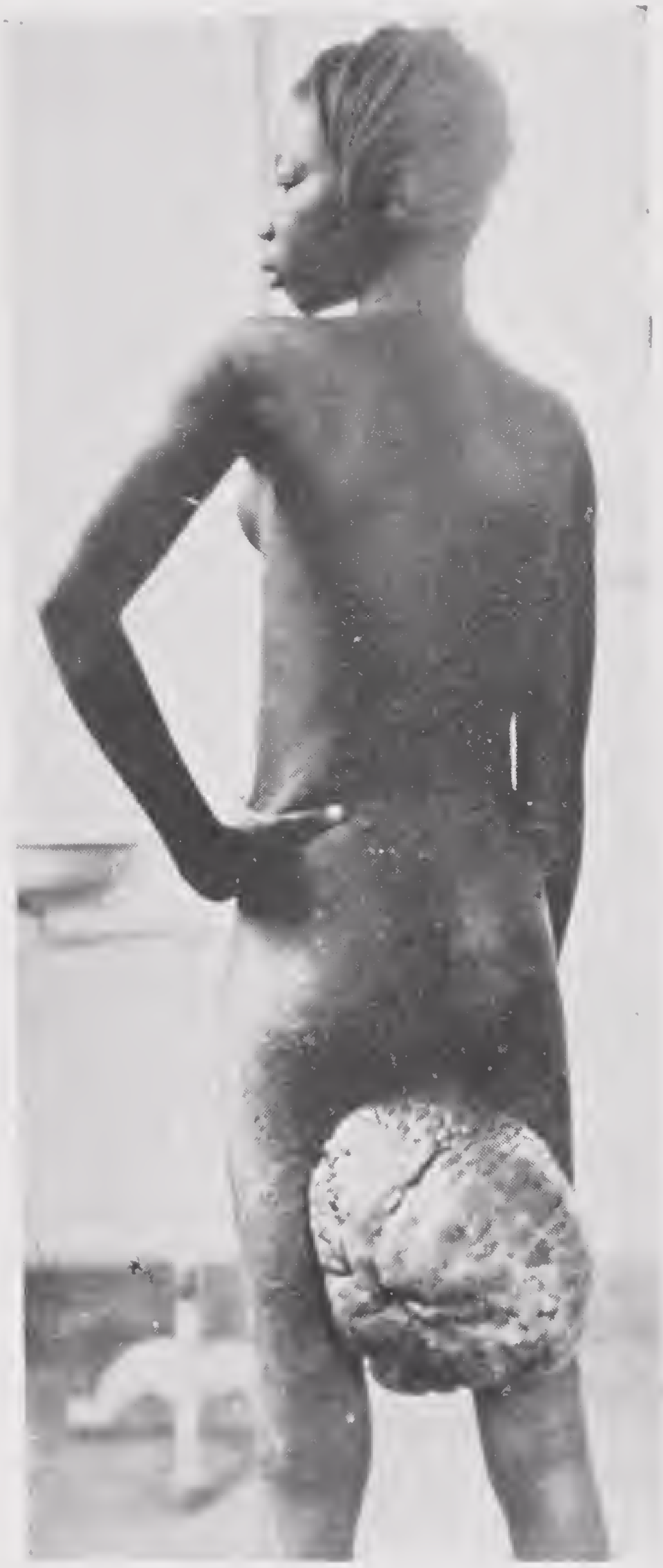

FIG. 82. GENITAL ELEPHANTIASIS OF THE WOMAN, CONGO
Coll. Tropical Institute, Antwerp

Whatever it may be, without pretending to solve the etiology of elephantiasis in which the filariae problably play an important part (*O* *volvulus*) or may be unique (*W. bancrofti*), we may proceed to its anatomic and clinical study.

Pathology: When we cut a fully developed elephantiasic scrotum, we notice first an epithelium, sometimes almost normal, sometimes proliferating; then a derma of several centimeters thickness, white, fibrous, easily cut; then underneath, corresponding to the subcutaneous spaces, we find a yellowish gelatinous tissue, almost liquid, more easily penetrated by the hand than by a knife. We have said that in the Congo the genital organs are normal to the touch; on the contrary, they are thickened and abnormal in regions where *W. bancrofti* exist.

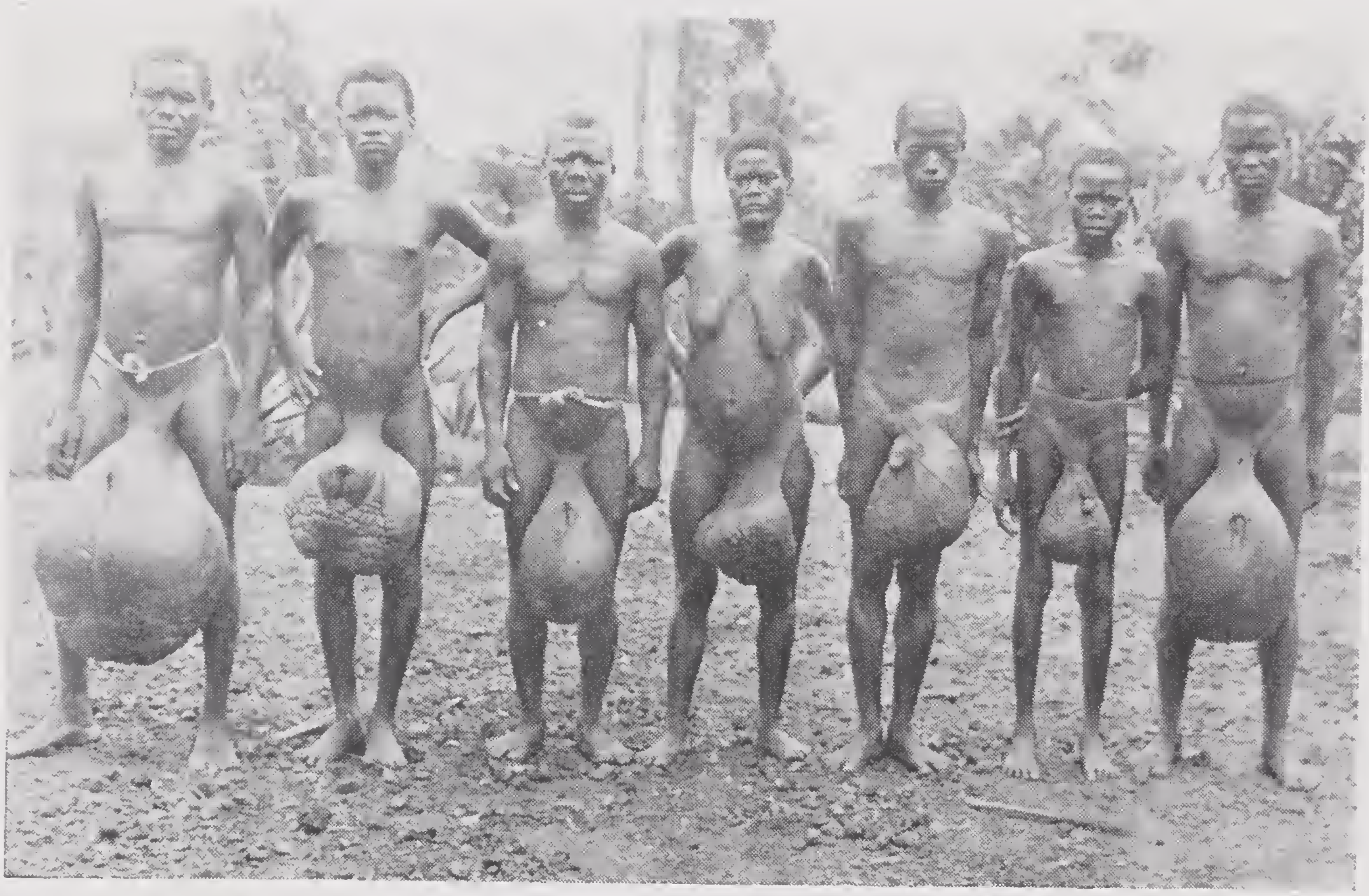

FIG. 83. ELEPHANTIASIS CASES FROM THE UELE, CONGO
Numbers 1, 2, 3, 6, and 7 are scrotal elephantiases. Number 4 is a female genital elephantiasis while number 5 is an inguinal hernia (coll. Tropical Institute, Antwerp)

At the beginning of elephantiasis, edema is of a light type with the phenomenon of the depression. At this point the microscope shows especially lymphatic dilatations. Then conjunctive hyperplasis begins with the multiplication of new fibroblasts and a certain degree of stiff cell infiltration.

Later, the conjunctive tissue becomes more fibrous, often with a homogenization of the collagen and rarefaction of the elastic tissues. At this state there is less edema and infiltration, although in certain forms of proved elephantiasis we sometimes find an abundant infiltration of neutrophiles and eosinophiles.

The pigment often shows anomalies of distribution (thick accumulations in the dermic histocytes).

Symptomatology: Illustrations have sufficiently popularized the affection to make long descriptions unnecessary. It is most frequently a disease of adults. In all countries it appears to be localized in the lower limbs. We rarely note the large elephantiasic limb, cylindrical with projecting cutaneous folds: more often the cutaneous hypertrophy remains moderate and lodged below the knee, the leg is cylindric, swollen with hard edema (except at the beginning when the edema hollows under pressure of the finger), the foot often has a dorsal thick cushion, the skin of the toes often presents a villous appearance. In the Congo, the indolence of the lesion is extreme. Genital localization, although rarer, attracts the interest of the patient more, and consequently of the physician. It is more often found in men than in women. In light cases there is a more or less notable thickness of the scrotum (about 10 cm. in diameter) under a free and normal penis, the testicles being ordinarily drawn up to the inguinal ring. On a more advanced degree, we have the classic tumor, whose weight varies between 5 to 6 and 30 to 40 kilos (and even 100), of pyriform appearance, with a more or less long pedicle and an opening at the outside surface which leads to the natural meatus. The testicles are held in the mass. The canal which leads to the meatus corresponds either to the prepuce (tumor appearing prior to the circumcision) or to the sheath of the penis.

More rarely we find a massive hypertrophy of the sheath of the penis often with strange shapes (trumpet, etc.). The scrotum has its share of hypertrophy but often moderately.

In women similar tumors, on one or two of the large lips, may sometimes come down lower than the knees.

Rarer localizations in the breasts, on the arms, even on the face are easily recognized.*

In primary elephantiasis, a condition most frequent in the Congo, the general health is very little affected. Large tumors seem to tire the heart. A combination of scrotal lesions and hernia is not unusual.

The evolution is slow, the established lesion is irreversible.

Prognosis is rather severe functionally. Moderate elephantiasis of the lower limbs incommodes very little (except esthetically) while, on the contrary, in the scrotal form, sexual inaptitude and hindrance in walking are rightly to be feared.

Diagnosis is easy. It suffices to notice the hernias and hydroceles which have made the skin thin and which have their own signs. Pseudo-elephantiasis of Schistosomiasis, of Nicolas-Favre disease, etc., have an entirely different appearance.

The etiologic diagnosis is more difficult; filaria, elephantiasis nostras, etc.

Treatment: Therapeutics for elephantiasis of the lower limbs have been rather unsatisfactory. However, a combination of very careful pre-treatment, methodical bandaging, rest in bed with feet raised, sometimes allows excision of the tissues to be of use. A long after-treatment similar to the pre-treatment is advisable.

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* On the scalp we must note cutis verticis gyrata, (an example of which we have seen on a Congolese woman).

Treatment of elephantiasis of the scrotum is one of the successes of tropical surgery. Its technic is as follows:

1. Rachianesthesia: Constrictive tube at the base of the tumor.

2. Liberation of the penis which is always easy to find and to isolate. One may maintain the channel which joins the external opening.

3. The tumor is cut through its middle and the testicles are isolated and raised with the penis in a compress on the pubic area.

4. Excision of the tumor, keeping a short cutaneous border level with the perineum and, in front, a scrap varying according to the quality of the skin. This scrap of skin will serve for the new sheath.

5. Careful hemostasis. We advise pinching of the arteries in the course of excision, for it is evident that when the tumor has been removed the constriction no longer functions. On the other hand, as this area does not allow compression during the final dressing, no artery must be left bleeding.

6. Plastic surgery of the new scrotum by sutures beginning at the perineum. The new sheath will eventually use the channel reserved when the penis was dissected.

The mortality rate is very low (less than 1 per cent) and relapses are rare.

In women the operation is a simple amputation.

13. DRACONTIASIS*

History: Dracunculus medinensis, producing dracontiasis, is the oldest known parasite. The term Dracontion appears in Greek texts dating from B.C. and referred to the serpent or dragon worm. Often called the Medine or Guinea worm, it has been described by Velsh in 1674 as *Filaria medina* and named by Linnaeus in 1758 *Filaria medinensis.*

Geographic Distribution: Africa (more especially Egypt, the shores of Lake Chad, of the Red Sea, the west coast of Africa), the Near East (Arabia, Iran, Turkestan), India (west coast and central part much more than in the eastern half), the Caribbean islands, the Guianas and Brazil. Ten cases were found in the U.S.A. (Chitwood), all of them either foreign or doubtful.

Etiology: The adult female lives in the subcutaneous or in deeper connective tissue. It measures from 75 to 125 cm. in length by 1.5 mm. in thickness. The vulva is atrophied and is situated near the head. The curved posterior end serves to anchor the worm in the tissues. The male is generally not found, its maximum length being 2.5 cm.

When the cephalic end of the adult female arrives near the surface of the skin, a papule is formed which later becomes vesicular and ruptures when it comes in contact with water. Motile larvae are discharged into the water. They measure 600 to 750 μ in length by 15 to 20 μ in breadth. Their anterior end is rounded and the caudal process is long and thin.

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* Synonym: Guinea worm; French: Draconculose, Ver de Guinée.

Transmission: The larvae of *Dracunculus* may live several days in water and up to three weeks in moist earth. They penetrate into the mouth of their intermediate host, a *Cyclops* (small white Copepode). They bore their way through the intestinal walls and undergo development in the body cavity. The metamorphosis is completed in ten to twelve days. In certain endemic regions of India as much as 37 per cent of the *Cyclops* are found to be infected.

Man becomes infected by drinking water containing infected Cyclops. The parasites liberate themselves and probably migrate through the walls of either the stomach or the duodenum and then through the tissues toward the subcutaneous connective tissue.

Symptomatology: The period of incubation is about one year, corresponding to the maturation of the worm, and is discrete or at most marked by vague local subjective signs.

The symptoms correspond with the arrival of the worm to the skin, generally of the leg. On the one hand they are general and in relation with the sensitization of the patient: light fever, urticaria, vomiting, asthmatiform dyspnea, etc. On the other hand we notice local redness, pain, vesiculation. The rupture of the vesicle frees the worm and the larvae. Unfortunately, there is very often a phlegmonous condition around the worm, due either to the "toxin" of the nematode or, more frequently, to an added infection. The joints may be affected by this process which is allergic as well as septic and ankylosis is the consequence. Other septic extensions have been noted.

Prognosis: There is a favorable "quoad vitam," especially if there are only 1 or 2 worms, as is often the case. But general or local complications may be serious. Among those infected in the province of Bombay, there are 23 per cent with arthritis. There is no immunity.

Diagnosis: This is difficult before the appearance of the worm. An x-ray examination may show up a worm especially if it is calcified (4 examinations on 20 Senegalese made at random by Delamare and Mouchet), or may also determine its position if lipiodol has been injected.

Treatment: There is no certain internal remedy against the parasite. The worm having perforated, the skin must be covered with a damp dressing. The worm will empty its uterus and the expulsion will be easier. This is obtained according to the ancient procedure used in the East: knot a thread of silk around the worm and roll it on a small stick gradually, every day, bit by bit. The entire extraction will take weeks.

Surgical extirpation is not advised on account of the meandering course of the worm through the conjunctive tissue.

Abscesses must be treated in the usual manner.

The arthritis can be drained by aspiration if the pus is sterile or after opening if there is an infection.

Prophylaxis: Personal prophylaxis is efficiently reached by boiling or filtering the drinking water. If the water is passed through a piece of cloth all *Cyclops* will be withheld and the infection easily avoided.

Social prophylaxis consists in preventing the larvae of *Dracunculus* from reaching the water, and in killing the *Cyclops*. The step wells where people are able to stand while taking their drinking supply should be abolished and replaced by narrow cylindrical wells with pumps rather than with buckets.

Quicklime or ordinary lime, copper sulfate, perchloron, and other chemical substances have been recommended for killing the *Cyclops* in the wells. The eggs of these Copepods, however, resist the action of these disinfectants, with the result that *Cyclops* reappear invariably within three weeks of treatment. One should therefore repeat the procedure every two weeks.

A fish, *Barbus puckelli,* which feeds voraciously on *Cyclops* and on *Dracunculus* larvae, has been introduced into some of the step wells in India.

DIFFERENTIAL DIAGNOSIS OF DERMIC MICROFILARIAE IN MAN

Dermic smears, stained with Giemsa (see also fig. 85)

	O. volvulus	*A. streptocerca*
1. Sheath	No Sheath	No sheath
2. Average Size	200 to 300 μ by 7 to 8 μ	240 μ by 3 μ
3. Posture of the Body	Rigid attitudes (iron wire)	Few undulations, almost straight
4. Posture of the Posterior Extremity	Often abruptly curved like a hook	Regularly curved (handle of a walking stick)
5. Characteristics of the Cephalic End	Rounded. Nuclei elongated and coarse	11 to 12 nuclei on a straight line or in quincunx, the four first oval, the other square
6. Characteristics of the Caudal End	Abruptly sharp pointed. Free of nuclei at the tip	Slightly and very progressively narrowing. Rounded and large somatic nuclei on one line and reaching a distance of 1 μ of the caudal end
7. Transmitters	*Simulium sp.*	*Culicoides sp?*

DIFFERENTIAL DIAGNOSIS OF BLOOD MICROFILARIAE IN MAN

Thick drops, stained with Giemsa* (see also fig. 84)

	W. bancrofti	*W. malayi* (after Brug, 1927)	*F. loa loa*	*A. perstans*	*M. ozzardi* (after MacCoy, 1933)
1. Sheath	Easily stained with Giemsa after alcoholic fixation	?	Easily stained only with hematoxylin	No sheath	No sheath
2. Average Size	300 μ by 8μ	225 μ by 8 μ	275 μ by 8 μ	100 to 200 μ by 4.5 μ	175 to 240 μ by 4 to 5 μ
3. Posture of the Body	Supple and elegant undulations	Undulations with secondary kinks	Short and sinuous undulations	Supple undulations	Large undulations
4. Posture of the Posterior Extremity	Straight	More or less straight	Curved on the body	Straight	Straight
5. Characteristics of the Cephalic End	Numerous small, round and well separated nuclei	Numerous nuclei	Numerous coarse, not well separated nuclei	Small, rounded nuclei, less numerous than in Bancrofti	?
6. Characteristics of the Caudal End	Progressively pointed but less sharp than in *O. volvulus*. Free of nuclei at the end	Two bulges on the level of two nuclei, one subterminal the other terminal	Very progressively pointed with a few elongated nuclei in the tip	Abruptly rounded off or truncated. Nuclei in the tip	Sharp pointed. Free of nuclei at the tip
7. Transmitters	*Culex sp.* *Aedes sp.* *Anopheles sp.*	*Mansonioides sp.* *Anopheles sp.*	*Chrysops sp.*	*Culicoides sp.?*	*Culicoides sp.*

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* Only the main characteristics as seen on thick drop preparations after the Romanowsky staining method (such as Giemsa) are given here. The position of the excretory cells and of the G cells is interesting only to the parasitologist. The tables and photographic plates on microfilariae were made at the Antwerp Institute of Tropical Medicine with the collaboration of A. Fain (*W. bancrofti*), L. Van Hoof (preparations), and R. Resseler (photography).

Fig. 84. →
(See also Chart, page 351.)

First row, above, *A. perstans microfilariae:* attitudes of the Microfilariae in 1 and 2, anterior and posterior extremity in 3 and 4.

Second row, L. loa.

Third row, *W. Malayi.*

Fourth row, *W. bancrofti* (phot. R. Resseler, Tropical Institute, Antwerp)

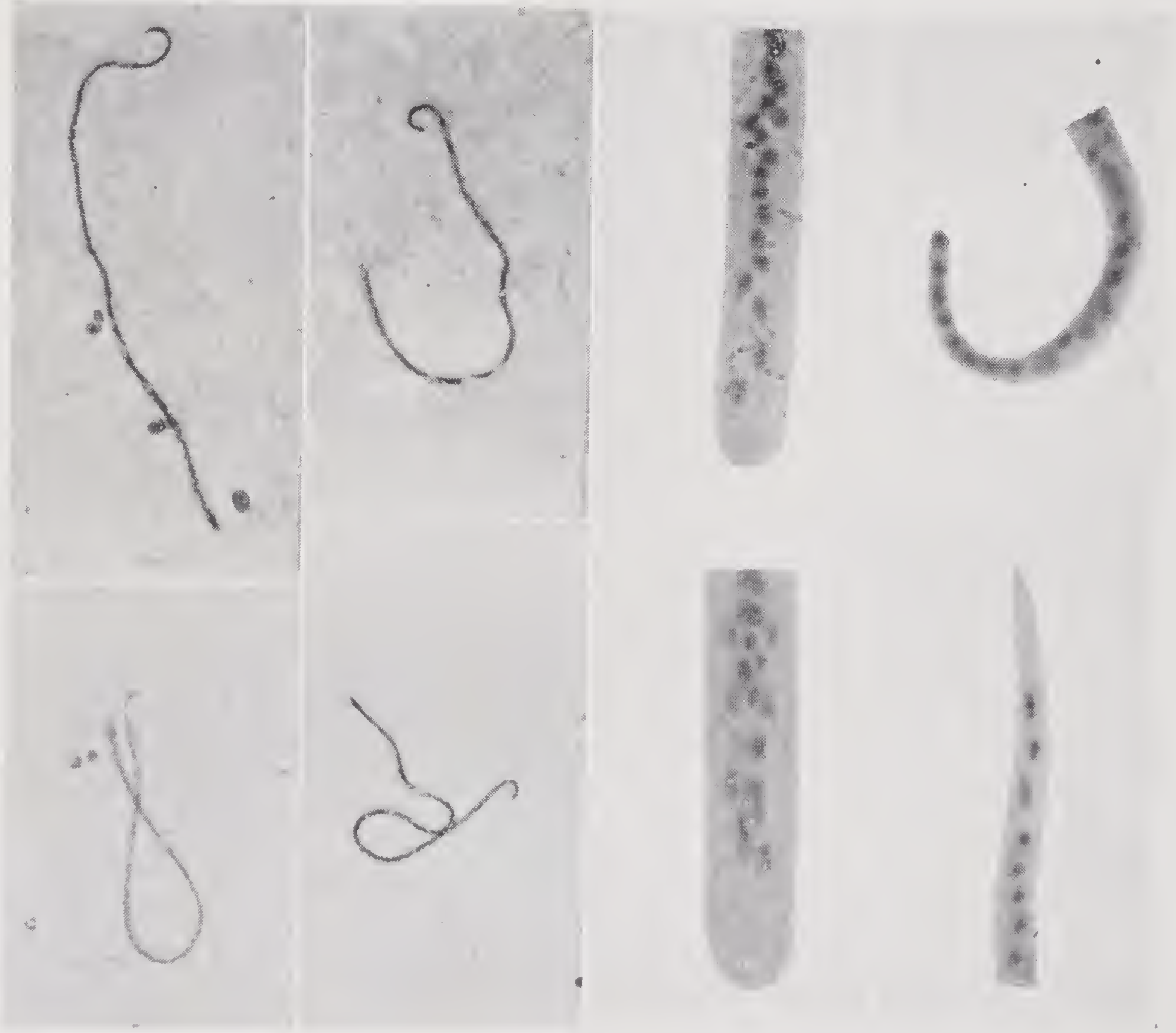
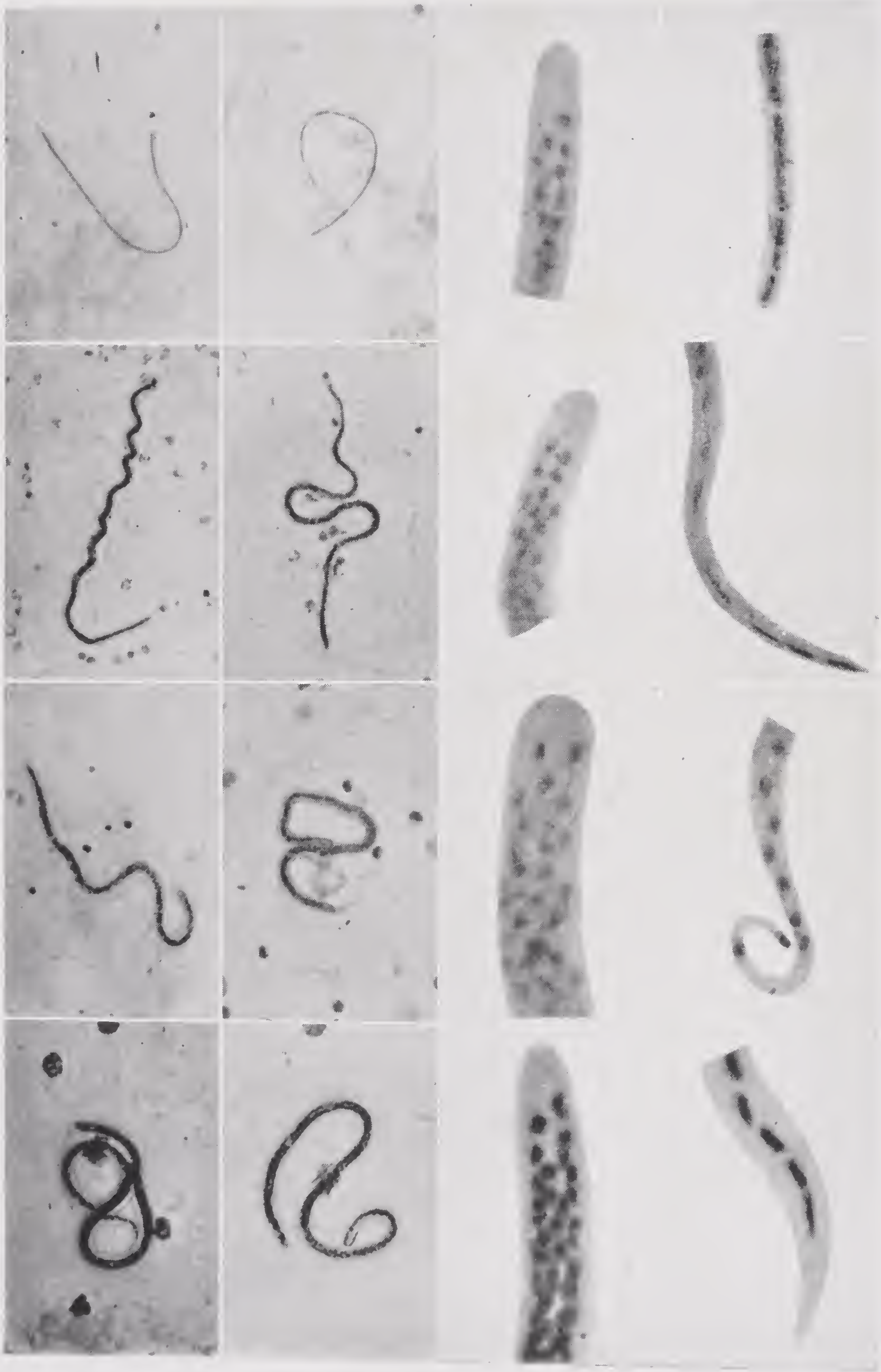


Fig. 85.
(See also Chart, page 350.)

Top row, *A. streptocerca.*

Bottom row, *O. volvulus;* stained with Giemsa in dermic smears (phot. R. Resseler, Tropical Institute, Antwerp). Due to differences in magnification, the *A. streptocerca* on the left appear larger than the *O. volvulus*, when actually the reverse is true.



Chapter VII

ACCIDENTS CAUSED BY ANIMALS AND PLANTS

We consider it unnecessary to discuss lesions caused by flesh eaters such as Carnivora, crocodiles, and fish, and by Ungulates. Undoubtedly, these accidents are more frequent in the tropics than in civilized countries but their treatment is in the field of general surgery. The study here will be made only of the venomous animals, together with a few remarks on the Myases and on venomous plants.

1. VENOMOUS INVERTEBRATES

Coelenterata: Polypus, and more frequently jelly-fish by their nematocysts, often cause painful skin rashes. They may cause delayed symptoms of dyspnea, eyewatering, coryza, discomfort and heartweakness.

Scorpions: The last abdominal segment of these Arachnids is a venomous organ with an additional curved chitinous spur. Dangerous species exist in various hot countries: North Africa, India, South America, etc.

Accidents are rarely fatal except in the case of children. Mortality is reckoned at 25–50 per cent. Symptoms resemble those determined by snake venom: local pain often transitory, general malaise, vomiting, dyspnea, convulsions in children. Treatment is the same as applied in cases of snake bites. In certain countries (Pasteur Institute at Alger) an anti-venomous serum is manufactured.

Spiders: The cheliceres of most spiders are furnished with venomous glands, but only certain species especially of the genus *Latrodectus*, prove dangerous to man (U.S.A., South Africa, Australia, etc.). In the U.S.A., out of 400 cases of bites by *L. mactans*, "the black widow," there were 16 deaths. The effect of its toxin on the muscles is very painful, causing muscular spasms comparable to the abdominal rigidity of peritonitis. There are no local lesions. *Glyptocranium* (South America) gives local gangrene. Treatment consists in applying warm, wet compresses, with injection of gluconate of calcium intravenously. An antitoxin also exists.

Myriapods: The primary pair of thoracic appendices of Chilopods are transformed into venomous hooks. In certain parts of the tropical world (Oceania), giant centipedes are feared for local and general accidents, even causing the death of children.

Diplopods (rounded millipedes having two pairs of appendices per ring) are inoffensive but sometimes a nuisance because of their mass migration.

Ticks: Bites of *Ixodes*, *Dermacentor*, etc., are accused of having caused in America, Australia, and South Africa deaths by ascendant feverish paralysis. Rapid extraction of the tick would cut short the phenomena and save life. The fatal cases were mainly encountered in children. The pathogeny is not known.

Insects: One finds venomous kinds among the Hymenopters: wasps, bees, drones, ants. The toxin inoculating sting is situated at the extremity of the abdomen. Symptoms are rarely more than local. Such as they are, they can be serious in cases where the glottis is stung, which may then swell dangerously. General symptoms sometimes result from multiple bites. Bees, wasp nests (especially the small arboreal African wasps) have often been the cause of serious trouble. Treatment of the skin involvement consists in applying weak solutions of ammonia. For the general symptoms, stimulants of the major functions are used.

Caterpillars: They sometimes determine urtication by means of their hairs which contain venomous glands. Certain Coleopters (Cantharides, Staphylinides) are vesicatory by their secretions.

2. VENOMOUS VERTEBRATES

Fish: One must note the species possessing a venomous spur either at the tail (certain skate), at the operculum (*Trachinus draco*), or at the fins (*Scorpaena*). Local and general symptoms are sometimes important.

Small fish have been reported as penetrating the bladder through the urethrum of bathers in Brazil (Amazon).

Among venomous animals one must cite, above all, the Tetradons of the Pacific, of which, if not the flesh, at least certain genital or digestive viscera possess violent toxins.

For some species of fish, toxic properties are related either to their nourishment or to special physiologic circumstances.

Lizards: The *Heloderma* of Southwestern U.S.A. are feared for their venomous teeth in the lower jaw. Death may result from their bites.

Serpents: We can eliminate from our studies the Boidae (American Boa and Python of the Old World) possessed of a powerful musculature but without venomous organs. The same holds for various other species. On the contrary, Colubrides and Viperides have dangerous venomous representatives of their families. We may consider as inoffensive, or almost so, aglyphic Colubrides which possess no venomous teeth, and opisthoglyphic Colubrides whose hooks are situated on the upper maxilla and, therefore, are not well designed for inflicting damage on man.

The "*Thanatophydia*" comprises:

1. Proteroglyphic Colubrides. Here the venomous apparatus is extremely perfected. The fangs are situated in front of the superior maxilla. These teeth carry on their anterior face a longitudinal groove which, in certain genera (*Naja*, *Dendroaspis*), succeeds by the conformation of its edges in forming an almost entirely closed duct. The excretory canal of the venomous gland (parotide) opens into its base. Any reptile having this particularity must be considered as dangerous. Furthermore, let us add that, observed at a distance, Colubrides are slender and agile, the head is oval, the cephalic region slightly separated from the body and the tail tapers progressively. These rough characteristics do not distinguish the proteroglyphic Colubrides from other adders.

If, in Europe, nearly all Colubrides are inoffensive, tropical climates possess some dangerous species: *Naja* (cobra), *Dendroaspis* (mamba), *Bungarus* (kraits).* *Najas* and *Bungarus* are extremely numerous in tropical Asia, other species of *Najas* and the *Dendroaspis* are African. Colubrides are rare in America but there exist certain species in Australia. Cobras are remarkable for the aptitude that they show in spreading their first ribs and thus forming the characteristic hood. To this group of Elapinae or terrestrial Colubrides is opposed the aquatic Colubrides, (Hydrophinae, sea-serpents), of small size with tail laterally flattened and with powerful venom.

2. *Viperids or Solenoglyphs:* The venomous apparatus here reaches its highest degree of differentiation. The curved-in character of the tooth transforms the groove into a closed canal, the true nature of which is shown by embryology. The fangs are well developed, curved and situated quite at the extremity of the maxilla. This bone, small and mobile, acts as a lever at the moment of biting, projecting the fangs. The gland holds an important reservoir of venom. The form of the body is usually less elongated than that of Colubrides. The triangular head forms a well defined and limited region. The tail forms an abrupt point.

The family Viperidae includes Vipers (Europe and Asia, especially the "Daboia" of India, the powerful viper of Russell) and the *Crotalus*, ("rattle snakes"), *Ancistrodon*, *Bothrops*, *Lachesis* of North and South America, *Causus* and *Bitis* of tropical Africa and the *Cerastes* from North Africa.

Pathogenesis: At the moment the serpent attacks, it opens the jaws wide, projects its fangs, and darts forward on its victim which it stings. Then it lifts the jaw, and thus the upper lip glands (paratids) are pressed by the masticatory muscles and by pressure the venom is projected through the excretory canal and the small duct or grooved canal in the teeth which is its continuation. The venom is a thin, yellowish or brown liquid drying like a varnished substance. Dissolved, it is easily modified (bacteria) but when kept dry can be preserved for a considerable time. Serpents produce it in varying quantities according to their species and size. A Russell viper could provide 100 mg. of dry venom, a cobra 300 mg., and an ordinary krait 8 mg. For humans a fatal dose would be 15 mg. (dry) of cobra venom and 42 mg. of Daboia venom. These figures vary, of course, according to circumstances. Venoms would be sapotoxins or toxalbumins. They are transformable into Anatoxin (toxoid) by the action of formol. They are antigens. Their pharmacologic action is infinitely variable but may be reduced to two principal actions, of variable importance according to species.

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*In parentheses, popular names in different regions.

1. *Cyto- and hemotoxins:* cellular necrosis, hemolysis, blood coagulation, modification of the vascular walls. These substances are particularly abundant with the Viperides: Daboia (blood coagulation), Crotales (hemorrhages), Bitis (local necrosis). They exist slightly in Colubrides and the Cobras, producing a local eschar. Diversely, *Crotalus terrificus* produces little reaction at the place bitten.

Hemolytic action is due to the transformation of lecithin into lysocythin by enzymatic action. The venom here appears as a phosphatase.

2. *Neurotoxins:* They act more particularly on nerve cells: vasomotor centers (Viperides), or on the respiratory center, motor centers, etc. (Colubrides). They are more thermostatic than cytotoxins. Pharmacologic properties of venoms have been used with relative success in therapeutics (Cobra venom as analgesic, Daboia venom as local coagulant).

Symptomatology: It is frequently observed that the bite reported by the native remains perfectly asymptomatic, during a sufficient course of observation. Either it is a matter of a slightly venomous serpent or of only a partial injection of venom. Local symptoms may be barely visible or simply subjective (pain). This is the case with many *Colubrides.* In other cases it is the contrary, and hemorrhagic edema, infiltration may be followed by heavy loss of substances (*Viperides*). Certain serpents (*Naja*) ejaculate their venom and thus cause a fairly mild conjunctivitis. Symptoms concerning blood, particularly with *Viperides*, are at times of hemolytic type: local hemorrhagic suffusions, prolonged bleeding of the bite, bleeding of the gums, hemoglobinuria. At other times, coagulatory properties provoke thrombosis and even sudden death by intravascular coagulation and embolism (bite given directly in a vein). The Daboias and kraits are redoubtable on this point. Finally the liver, kidney, and brain may show modification of tissue due to cytotoxin and concomitant clinical phenomena. Neurotoxins are responsible for circulatory symptoms, hypotonia, weak pulse, general weakness, cold sweats and respiratory symptoms, dyspnea, vomiting, paralysis and multiple nervous signs, such as dread, troubled sight, paralysis, hypothermia.

Prognosis is highly variable. In the Congo, many doctors have practiced for years without seeing deaths. One of us (A. D.) has seen a fatal collapse twenty-four hours after the bite of a Bitis. Had the subject lived, he would certainly have had an extensive gangrene of the bitten arm. Involuntary delay in consulting rendered any form of therapeutic hopeless. In India, serpent bites cause a fairly important mortality. Snakes there are especially redoubtable (Daboias, Cobras, kraits) particularly because of the density of population.

The United Fruit Company (tropical America) has had among one hundred thousand workers, 23 subjects bitten, and 1.6 deaths annually.

Diagnosis: The mark of the fangs is diagnostic and can, by its appearance, suggest the species, and, by the spacing of bites, the animal's size. An appearance of local inflammation and bleeding with marked abundance of bloody oozing at the site of incision must indicate a diagnosis of vipers. It sometimes occurs that the victim brings the offending snake to the clinic with him.

Treatment: Prompt intervention soon after the accident is vital. One must:

1. Prevent the venom from being absorbed, by the use of a tourniquet applied for thirty minutes to one hour maximum. The wound should be incised, or better still, sucked or even excised under local anesthesia.

Without, however, decisive experimental basis, it seems advisable to apply solutions of potassium permanganate 1 per cent on the incised wound or to inject this solution surrounding the inoculation. This latter system is perhaps more active but there is risk of local disorder. Gold chloride 5 per cent seems preferable to permanganate. We also quote the use of auto- or isoblood (10–20 cc.) used to infiltrate the region and fix the toxins. This method is less objectionable and could be tried in the case of facial bites.

2. Neutralization of toxin by anti-toxin serums, either specific if the species has been identified, or polyvalent by choice according to the country and its fauna (10 to 20 cc. serum).

3. Maintain the major functions.

Prophylaxis: Wearing of high boots each time one walks in long grass, never walk at night in slippers around the house.

3. MYASES AND OTHER PARASITIC INFESTATIONS

By this is meant pathologic phenomena related to the development of Muscidae larvae in the human body.

Myasis of wounds and natural or accidental cavities.

It is not uncommon, especially in warm countries, to see wounds or accidental cavities overrun by fly larvae. At the level of simple wounds it is not so important, as the larva preferably attacks dead tissue. Furthermore, ordinary care of wounds is sufficient to stop the development of larvae. The cleansing action of *Lucilia* larvae has been used in surgery. The methods seem, however, to have been forgotten. It is known that healthy tissue is not always spared. At the level of natural cavities (nose, ears, eyes) the symptoms may be more serious and cases have been cited in particular of invasions of the frontal sinus, orbit, etc. The larvae in question belonged to different species: *Chrysomia bezziani* (old world), *Cochliomya americana* (America), *Lucilia sericata* (cosmopolitan), etc.

Cutaneous myasis: creeping and furunculoid. Here development progresses in the thickness of the skin. It can take the form of creeping myasis with ecchymotic and painful passage, due to Oestridae (see also section on Ankylostomiasis). At other times one observes furunculoid tumors caused by Oestridae but more frequently in hot countries by larvae entering directly into a hair follicle (*Cordylobia anthropophaga* or "Cayor worm" in Africa, *Dermatobia cyaniventris* in America).

Hematophageous larvae: The larva of *Auchmeromyia luteola*, an African fly, lives on or in the soil of huts and bites man at night.

JIGGER FLEA

*Tunga (Sarcopsylla, Dermatophilus) penetrans.** Males and nonfecundated females live in the ground of houses, etc., in Africa and tropical America, attacking man as other fleas do. The gravid female penetrates into the human (or animal) epidermis, especially between the toes, and in a few days develops its eggs, becoming a small, rounded white mass reaching a few mm. in diameter. Intense itching characterizes the beginning of this invasion and with normal men limits the evolution. Lunatics and advanced sufferers of sleeping sickness often let themselves be overrun by numbers of these parasites. Infectious accidents are fairly frequent in certain countries. In the Congo they are rather rare. The remedy is simple; extraction of the female without breaking it, swabbing out the epidermic cavity (which bleeds easily) with iodine. Prophylaxis lies primarily in meticulous cleaning of the floor boards with water; also the wearing of shoes.

POROCEPHALES

Armillipes armillatus: (Family of Linguatulidae, Arthropodes.) This parasite is often encountered during autopsies in Central Africa. The adult, vermiform by adaptation to a parasitic existence, with a ringed body, is found in the respiratory ducts of Pythons (definitive host). The encysted nymph is often found in man: liver capsule, peritoneum, visceral pleura. It is incurved and also of annulated appearance. The infection of man (intermediate host) probably occurs by ingestion of eggs expectorated on plants (van den Berghe). Pathogenic action is null.

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* French: puce chique.

4. VENOMOUS PLANTS

We shall cite only a few plants having a certain social importance or creating characteristic syndromes.

Indian Hemp, Cannabis indica, Hashish. This plant is widely consumed in the Middle East and in Africa. In the Congo, it is known under the name of Diamba or bangi, and Bhang in India. According to the country and the manner of preparation, the active substance is sometimes absorbed and sometimes smoked. It produces a euphoric state, hallucinations, at times erotic, stupor and craving. It can lead to marked psychic weakening. Its action is ill-established in the Congo. Lepers willingly make use of it. Hemp appears to be only slightly toxic.

Cannabis Sativa, Marihuana. Plays a similar role in Mexico and the U.S.A. It is used in cigarettes, sometimes in addition to opiates. Here again euphoria, sexual hallucinations, the suppression of inhibitions characterize the intoxication. Fits of nervous anxiety have also been observed. The problem is well known to the public authorities.

Opium. The use of this drug by ingestion (in Persia, India) or by smoke (Far East) is sufficiently well known and requires no further comment. Civilized countries seem to exhibit a preference for morphine, etc.

Cocaine. The same may be said of a South American plant (*Erythoxilon cocoa*) whose action has been defined by European pharmacology and toxicology.

Mescal, Peyotl. A drug used by the North American Indians which provokes, in addition to the symptoms caused by hemp, excitation of the psycho-optic zone with colored hallucinations.

Lathyrism. This is a spastic paraplegia observed in Algeria, India, etc., attributed to the eating of beans (*Lathyrus sativus, cicera* and *Klymenum*). It seems that this leguminous plant is toxic when eaten in excess. The real pathogeny of accidents is rather obscure: intoxication, deficiency, intoxication by plants used with the main plant, particularly *Vicia sativa angustifolia.* In the Kwango (*Congo*) an epidemic of spastic paralysis broke out a few years ago, the cause of which has not been defined.

Akee Poisoning, Jamaica Vomits. This intoxication is not well understood. It is believed that it is also provoked by a hemolytic saponine contained in unripened fruits of *Blighia sapida.* Fairly numerous accidents are observed in the Antilles. Ripe fruit is not toxic.

Favism has been discussed with malarial hemoglobinuria.

Epidemic Dropsy (intoxication by *Argemone mexicana*). See further, Vitamin Deficiency.

Dermatitis venenata. Numerous plants can cause erythematous or nettled dermatitis. Some cause a direct toxic effect, such being the case with an African "itch," caused by various *Mucuna* leguminous plants. At other times there is sensitization, and complications appear only with certain subjects, as is the case in Europe with *Primula obconica.*

Khat, Cafta, Miraa. Catha edulis is an African tree whose leaves and branches are chewed, infused, smoked, etc. Produces euphoria, eliminates fatigue and hunger, sometimes causes excitement, spasticity, and more or less persistent brain disorders. Should be checked, in view of the tendency to Khatomania (E. Africa).

Kava. Nonalcoholic, intoxicating drink derived from *Piper methysticum* (Polynesia) and drunk on feast days.

Jengkol. The beans of this edible Javanese vegetable strongly irritate the kidneys and can produce albuminuria and anuria. Urine contains crystals which are probably the cause of complications through crystalluria (De Langen).

Mandioca poisoning. It is useful to bear in mind that certain foods can be toxic because of improper preparation. Bitter manioc (*Manihot utilissima*) contains a cyanogenic glucoside. It must be crushed and washed before use in order to hydrolyze the glucoside. There are also very toxic false yams.

Chapter VIII

AVITAMINOSIS, DEFICIENCY DISEASES

Deficiency diseases are not peculiar to the tropics. Wherever humanity is poor, agriculture rudimentary, and the diet monotonous, various troubles pertaining to nutrition soon appear. Such conditions and the diseases they imply are frequently seen in the tropics.

The concept of vitamin, dimly suspected as early as 1881 by biochemists of the Bunge school, has developed through the work of Eyckman and Gryns in Batavia on experimental polyneuritis of the hen (1890–1897) and also through the work of Hopkins, in England, on the alimentation of rats (1906–1912). The term "vitamin," chemically incorrect, goes back to Funk (1911) and has taken root in the language.

For the physiologist of the present time, vitamins represent molecules, which the organism cannot synthesize, indispensable to its vital balance and which do not intervene as a source of energy or in the structure of the protides. This last remark differentiates vitamins from exogenous amino-acids which also must be found in the diet. Vitamins frequently take an important part in the making of ferments and therefore in the catalysis of metabolism.

One must not lose sight of the fact that avitaminoses are often incomplete, and, on the other hand, complex. Furthermore, poor populations are exposed to suffering from total inadequacy of diet (starvation or semi-starvation) or inadequacy in quality or quantity of proteins. These last conditions seem to be frequent in Central Africa (malignant malnutrition of English authors).

One can distinguish primary avitaminosis due to lack in the alimentation and secondary avitaminosis due to intestinal nonabsorption or to some other endogenous cause.

The general etiology of avitaminosis is mainly of economic order: poverty, ignorance of agriculture, and therefore lack of variety in products. However, agriculture, even if it is progressive, is also dangerous if it is too highly specialized toward products inadequate for proper nourishment. Experience shows, then, that producers have a tendency to buy food that is more abundant and more economical, but quite often also poor in vitamins.

Civilization, too, can be a cause of avitaminosis: exaggerated bolting of flour excess of canned food, etc.

Predominance of avitaminosis has always been noticed among collectivities whose diet is governed by administrative rationing: prisons, armies, labor, etc. It is easy to understand that it is less difficult to provide calories which can be bought wholesale than vitamins. The latter are always, to a certain degree, a luxury. The part played by war, sieges, lengthy sea travels without ports of call, is obvious.

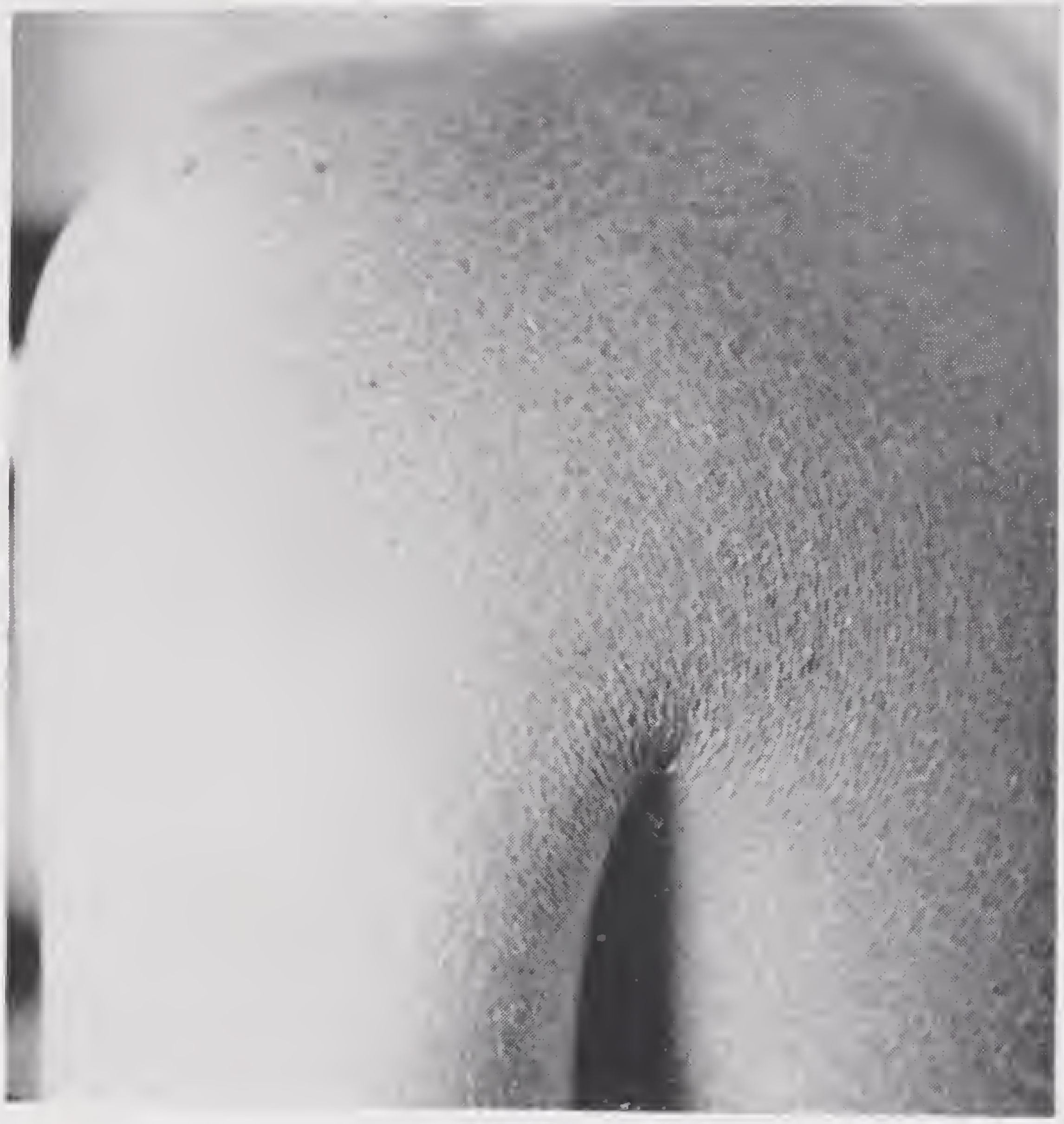

Fig. 86. Xeroderma Due to Avitaminosis A
Courtesy Dr. Howard Rapaport and Dr. Harold Herman

It is classic to divide vitamins into liposolubles and hydrosolubles. The first follow fats as they are mechanically extracted or chemically extracted, the second are extracted with water or hydroalcoholic solutions.

Let us mention that the chemical methods of vitamin dosage in the blood, the urine, etc., can help diagnose avitaminosis.

1. LIPOSOLUBLE VITAMINS (CYCLIC NUCLEI WITH CHAINS OF ISOPRENE)

A. Vitamin A—Axerophthol—Antixerophthalmic Vitamin $C_{20}H_{29}OH$

Physiochemical Characteristics: Axerophthol is found in the unsaponifiable fraction of fats. It resists rather well to 120 C. of heat in the absence of O_2, and also to preservation, but is sensitive to oxidation, to light, and to acids.

Ternary molecules derived by hydrolysis of the carotene $C_{40}H_{56}$ (α,β,γ) which is the pro-vitamin transformed in the liver into the active product.

International unit: It is equivalent to 0.6 γ of beta carotene.

Physiologic action: The main function is to maintain the epithelia in good order. In deficiency the latter alter and are an easy prey to infection, from which may come the old term of anti-infectious vitamin. Axerophthol intervenes in the regeneration of retinal purpura. In young animals, growth is inhibited by its deficiency. Axerophthol is also a regulating factor of metabolism (thyroid, liver).

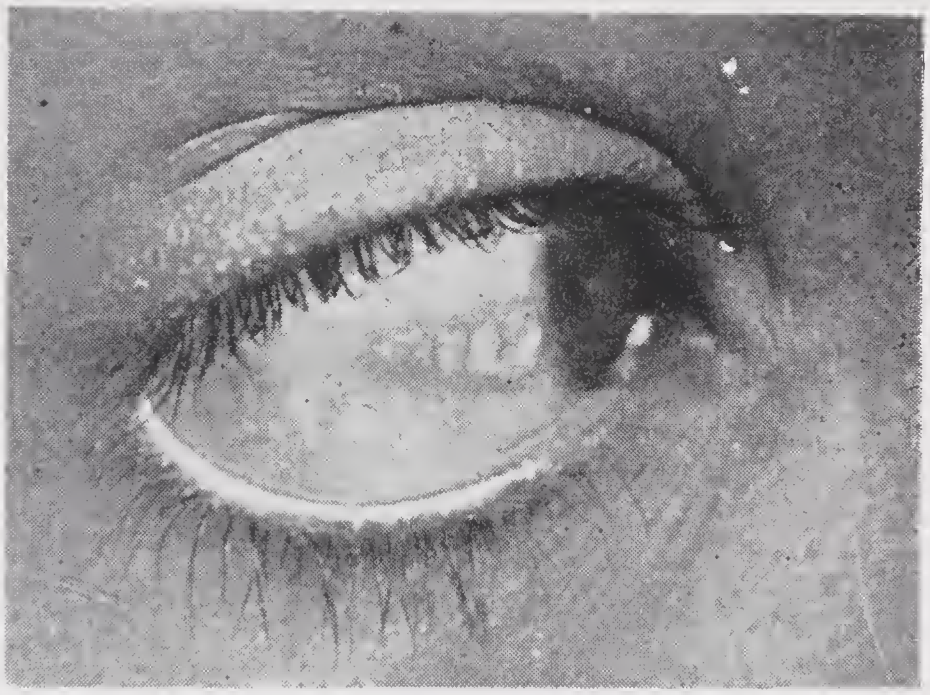

FIG. 87. BITOT SPOT
Triangular spot, base reaching the corneal margin and the surface covered with white adherent foam. Tamil boy, 10 years (Courtesy Dr. P. Fascal)

Experimental animals: Young rats are mainly used (weight, xerophthalmy, vaginal keratosis).

Human pathology: Although most of the epithelia can suffer from deficiency in vitamin A and show atrophy or keratinization, clinical phenomena are mainly observed in the eye. Hemeralopia* is a more or less precocious sign and can be investigated under conditions of darkness.

Xerophthalmy attracts a greater degree of attention. It manifests itself by abnormal feelings in the conjunctivae, then by a thickening of the conjunctiva with yellowish pigmentation. One observes whitish spots and Bitot's spots and the cornea may, in the end, become quite soft and infected (keratomalacia, perforation). In certain countries of the Far East

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* Hesperanopia is a more exact term.

(Southern India, China) cecitis is not rare, the lesions being often bilateral, brought on through a complete deficiency.

In the skin, the following manifestations have been related to vitamin A deficiency: phrynoderma (toad skin), dryness (xeroderma), follicular keratosis (arms and thighs at the extension, legs at the flexion) to be differentiated from scorbutic papulation by the absence of small hemorrhages. Lesions of the mucoses are also attributed to this deficiency. They range from slight bronchial alterations to pyelo-nephritis, cystitis, renal calculosis, etc. Further studies appear necessary.

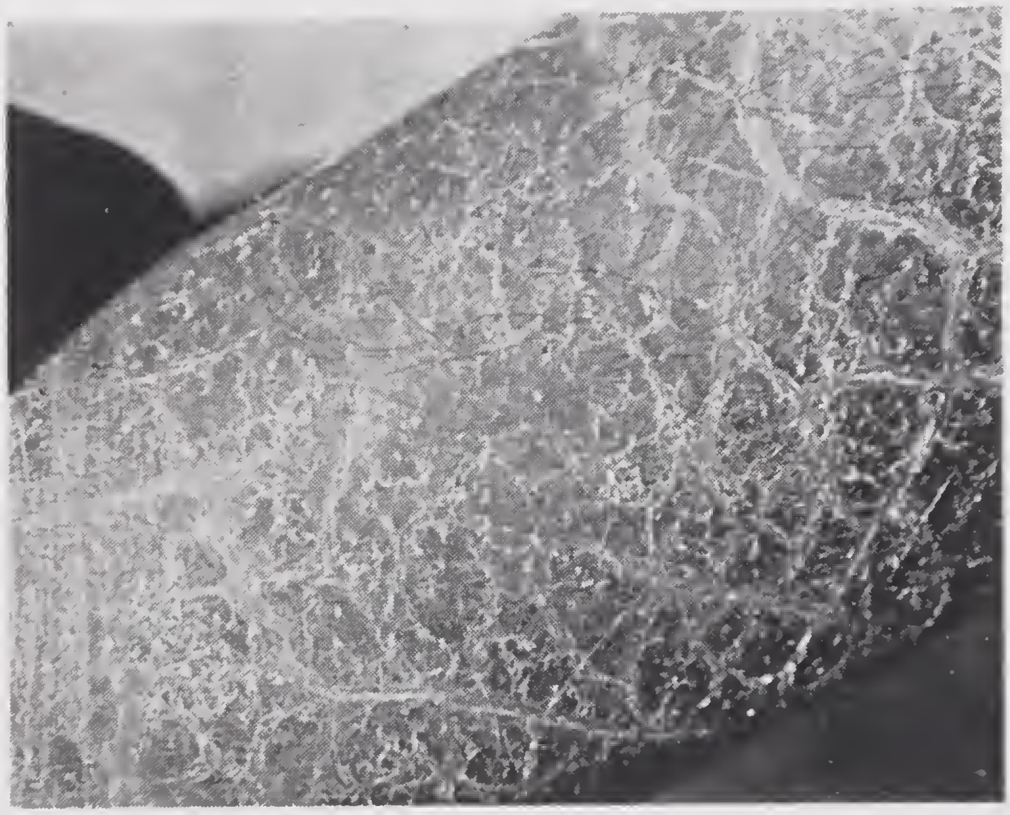

FIG. 88
Ichthyotic appearance of the skin of a Tamil boy with vitamin A deficiency (Courtesy Dr. P. Fascal)

The susceptibility of various races to pneumonia has also been attributed to insufficiency of axerophthol (very questionable).

Colorimetric dosage (by $SbCl_3$) can be done either in oils or in the blood where there would be 40–50 γ of the product per 100 cc.

DISTRIBUTION OF VITAMIN A IN NATURE AND PROPHYLAXIS

Green, red, or yellow vegetables are generally rich in carotene ($C_{40}H_{56}$). This pro-vitamin is transformed by normal livers into vitamin $C_{20}H_{29}OH$. The carotinoid substances are abundant in the vegetable kingdom. In Africa, palm-oil is a valuable source.

Animals accumulate the vitamins in the liver and the kidneys. Some go into the milk (butter), especially in the colostrum. The liver oil of fish (cod, halibut) is particularly rich (plant origin to be found in plankton).

Daily need of the adult is set at 3.5 mg. to 5 mg. of Beta-carotene, or 1 to 2 mg. of vitamins, or 25 to 100 Gm. green vegetables, 60 Gm. carrots, 50 Gm. of liver or butter.

Artificial or therapeutic source: Commerce provides fish-oil of great activity. The toxicity of the vitamin seems slight or even nul.

Deficiency indications: Hemeralopia, xerophthalmia, urinary calculi, leucorrhea, Basedow's disease (vitamin A is antagonistic to thyroxin). The therapeutic dose is from 10,000 to 80,000 I. V. a day.

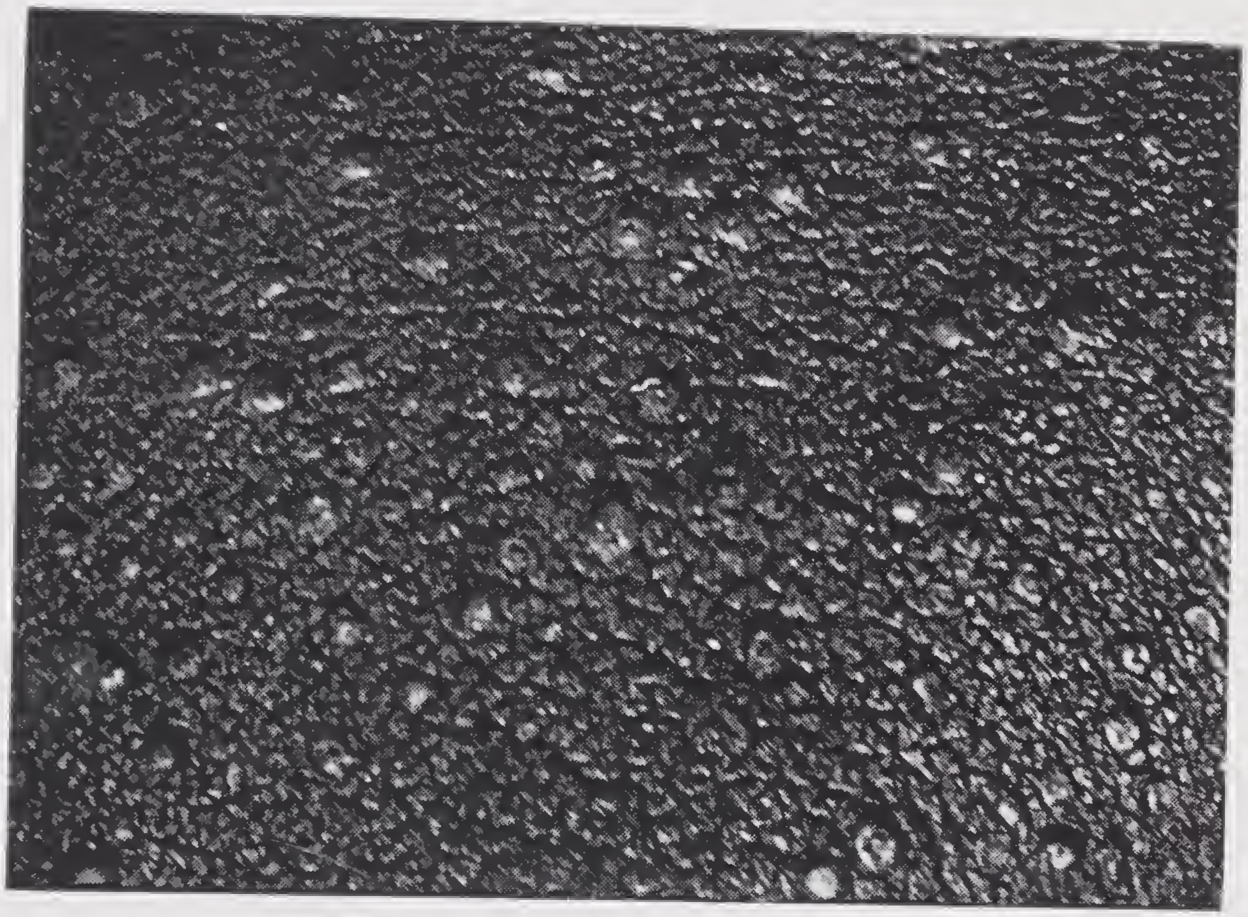

FIG. 89. PHRYNODERMA (TOAD SKIN)
Large, flat hyperkeratonic papules on the elbows of a Tamil boy (Courtesy Dr. P. Fascal)

B. VITAMIN D OR CALCIFEROL, NATURAL OR ARTIFICIAL, ANTIRACHITIC VITAMIN

The irradiation of the skin transforms epidermic sterols into vitamin D. This probably explains the scarcity of rachitism in tropical lands (exceptions due to special modes of life: cloistered life in harems, etc.). The disease being cosmopolitan, we do not think it necessary to develop the subject here.

In the Congo, obvious rachitism with deformation of the bones seems to be very rare. However, obstetricians often notice a slight flattening of the pelvis, the etiology of which is not definitely known. Eutocia which is so common among black women would really be due mainly to the fact that the fetus is of a relatively small weight at the time of delivery.

C. VITAMIN E OR TOCOPHEROL

$C_{29}H_{50}O_2$ is related to fecundity. Its part in the depopulation frequently observed among tropical tribes is not clearly defined. Some observers have incriminated in certain regions of the Congo either hypoplasis (testicular) or the rather frequent azoospermia. These facts, however, are not sufficiently established and it would not even follow that avitaminosis is responsible. A diet containing green vegetables seem sufficient to bring the necessary quantity of vitamin E, which, in periods of child-bearing, reaches 2 to 5 mg. a day.

Vitamin F: Linoleic acid: This unsaturated acid must be considered as a vitamin among rats (cutaneous accidents). Its role in human dietetics is unknown.

Vitamin K or Phylloquinone: This vitamin of coagulation (synthesis of prothrombin) does not specifically interest tropical pathology either.

It has been prescribed in malarial hemoglobinuria with apparent success. To our knowledge, a lack of prothrombin is not reported in that illness.

2. HYDROSOLUBLE VITAMINS

Hydrosoluble vitamins appear much more in the pathology of tropical lands and we shall study three diseases of importance: Beriberi (avitaminosis B_1), pellagra (deficiency in nicotylamide), scurvy (deficiency in vitamin C, acid l. ascorbic).

These hydrosoluble vitamins are extremely varied chemically.

A. GROUP OF THE "B" VITAMINS

These are extracted from the liver, yeasts, etc., from substances with a vitaminic action that experimentation has more or less divided in a series of substances among which many have been chemically characterized.

(a) VITAMIN B_1, THIAMIN, ANEURIN

This vitamin, known since Eyckman's work at the end of the last century, is the thermolabile factor of extracts of yeast.

Physicochemical characteristics: This sulfurous organic substance (containing a thiazol nucleus and a pyrimidin nucleus) crystallizes in colorless crystals and in the shape of a spearhead. The substance is quite soluble; the solution is rather stable in an acid environment and can then resist to a short ebullition. It is little oxidable and is found in the grains of cereals.

A salifiable amine link allows it to be used in the form of chlorhydrate and a primary alcohol link is esterifiable.

International unit: 3 γ of the crystallized product.

Physiologic action: Pyrophosphoric ester of aneurin is the co-ferment of carboxylasis (ferment separating α ketonic acids). In this respect vitamin B is indispensable to the metabolism of the glucides. It plays a part in the decarboxylation of pyruvic acid CH_3COCO_2H, CH_3COH (acetaldehyde) and from there into the synthesis of glycogen. Therefore, there is an increased need during muscular work, fever, etc. Inhibiting cholinesterase, it reinforces the action of acetylcholin. Urinary elimination varies; it must normally reach 12 units a day.

Experimental animals: Hens, pigeons, rats are commonly used. Fowl present a deficiency polyneuritis. Fowl beriberi shows hypothermia, ataxia, muscular cramps, opisthodonos, brachycardia.*

Natural sources: (1) Vegetal (presence of thiamin): rice-bran and cereal-bran, grains (whole) and food derived from it, yeast, and in small quantities in most fruits and vegetables.

This vitamin is widely found but not in large quantities. White bread contains one-tenth as much aneurin as whole bread and one-hundredth as much as wheat germ.

(2) Animal (presence of pyrophosphoric ester): flesh-meat (little); heart, liver, and kidneys are richer. Milk is poor. There is some in the yolk of eggs; 100 cc. of blood contains 8 to 16 γ.

Daily needs: 1 to 2 mg. or better, 1 mg. per 1,000 food calories. This represents 1 to 2 Kg. of meat or 300–600 Gm. of liver or kidneys, 2 to 5 liters of milk, 1 to 2 Kg. of cabbage, 200 to 300 Gm. of whole wheat or 100 Gm. of cereal germ. It is obvious that vitamin B_1 is not abundant. Pregnancy and nursing double or treble these needs.

Artificial sources (therapeutic): Chlorhydrate of thiamin is sold in any required quantity by pharmaceutical firms. Its toxicity is nul.

Deficiency indications: Beriberi, polyneuritis, alcoholic myocardosis, diabetes, in all cases of considerable use of sugar.

Beriberi (Polyneuritis Epidemica)

Definition: Avitaminosis B_1, characterized by polyneuritic troubles and, or, by circulatory disorders and edema.

HISTORY

The disease was described in Java by Bontius, as early as 1642. Eyckman and Gryns did historic work at the end of the nineteenth century, also in Java, on experimental polyneuritis of hens. These authors recognized that hens fed on polished rice developed an illness characterized by paralysis while rough rice or rice-bran prevented the appearance of the illness or cured it. The concept of vitamin, however, was not yet evident and Eyckman thought that some form of counter-poison existed in the bran.

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* Recently a Thiaminase which splits vitamin B_1 in Thiazol and Pyrimidine has been discovered in certain fish (Chastek and colleagues, Abderhalden). Pigeons fed with viscera of these fishes (carp, etc.) develop an acute beriberi.

GEOGRAPHIC DISTRIBUTION

Although principally known in the Far East (predominant use of rice), the illness has also been observed in tropical and temperate America (Labrador, Newfoundland), in Mesopotamia (Siege of Kut el Amara, 1916), in the Congo, etc. A nautical beriberi has also been noted.

ETIOLOGY

Infectious theories no longer find credit today. Beriberi often appears as an epidemic when a large number of people share the same diet or the same mode of life, or when some infection, making the need of thiamin greater, reveals a latent beriberi among a generally deficient population.

The meaning of deficiency in vitamin B_1 results from: (1) experiments, mentioned above, done by Eyckman; (2) epidemiologic research made in various countries and especially in Indonesia by Vorderman. Beriberi used to strike about 3 per cent of the prisoners fed on polished rice, against 0.01 per cent in collectivities using rough rice. Furthermore, prophylaxis based on the abandonment of polished rice has proved its worth everywhere. (3) Experiments of Fraser and Stanton in Malaya (1911), and of Strong and Crowell (1913) in the Philippines, on human subjects with well established diets.

It appears from all this research that the type of beriberigenous food is constituted by polished rice (Far East), or very white flour (Newfoundland) with fats and often a deficiency in, or only canned, meat. If to this are added causes necessitating the use of thiamin (muscular work, very high consumption of carbohydrates, fever, pregnancy), beriberi tends to occur.

Rice: When gathered, and still coated with glumes it is the "paddy," which can be stored well but is unfit for consumption. Beaten and roughly sifted, or sifted after a short heating with steam (parboiled rice) it retains a part of the colored film that surrounds the grain and which is the "unpolished rice." Polished at the cylinders, it becomes completely white, deprived, as it is, of the layer of aleuron rich in phosphorus and of the germ. It is the "polished rice" the conservation of which is so remarkable in opposition to the unpolished rice easily attacked by insects or mouldiness.

Polished rice blackens completely by the action of Lugol: on the contrary, if the film remains the color is not very dark. The Buitenzorg (Java) station provides a chart of standards of coloration. One can also make the dosage of P_2O_5 which cannot fall below 0.4 per cent.

"Hungarian" white flour, appreciated for its ability to be stored well, is also very deficient. Bread contains yeast, which slightly raises its content in vitamin.

Next to primary avitaminosis, i.e., by lack of the product in the diet, is secondary avitaminosis, i.e., endogenous: intestinal and hepatic troubles. Excessive usage of alcohol predisposes to deficiencies, probably because of the abnormal diet and also because of the lesions of the digestive mucous membranes. In addition, alcohol necessitates aneurin for its metabolization.

PATHOGENESIS

Lack of thiamin blocks glucidic metabolism at the pyruvic stage. As a result, an excess of the acid is found in the blood, muscular tissues, and nervous tissues.

Muscular fibers of every type alter: hydropic dilatation of the sarcoplasm. It is possible that the (nonspecific) alteration of the nervous fibers is of the same origin. This lesion amply explains the cases of paralysis, etc.

As for heart disorders, the genesis could be due to a deficiency of the arteriolar musculature, bringing about the engorgement of the veins and the right heart. The fibers of the heart, also altered, allow the myocard to dilate with a possibility of secondary valvular deficiency (Wenckebach).

PATHOLOGY

Macroscopically, one notes mainly the dilatation of the heart, especially in its right part, with the wall thicker also. There is stasis in the liver but not in the lungs. A certain amount of pericardic exudate is the rule.

In the brain, edema and congestion of the parenchyma as well as of the meninges are accompanied by small hemorrhages.

The digestive viscera are congested and particularly the wall of the gall-bladder is found to be edematous.

Microscopically, muscular fibers of the heart and sometimes of the limbs present interstitial edema, vacuolization of the fibers, either in rather important cavities, or in small nonlipoidic vacuoles. The striation can be altered and there can be a multiplication of muscular nuclei and of interstitial tissues.

The nervous cells present different alterations. The nervous fibers are degenerate along the sheath and the axone, with a multiplication of the schwannian and conjunctive nuclei.

SYMPTOMATOLOGY

The incubation is generally long, often two or three months, according to the degree of deficiency which is never absolute. There is scarcely any important reserve of thiamin in the organism. A subject in a state of complete inanition does not die of beriberi; his vitamin needs are, moreover, greatly reduced.

Phenomena of invasion of a toxi-infectious aspect have frequently been described. They are probably intercurrent diseases which provoke avitaminosis. On the other hand, digestive troubles, lack of appetite, dyspepsia, constipation are definitely related with illness and are due to atony of the smooth fibers. The same applies to the general weakness and neurasthenic aspect of the patient.

Description of the illness generally divides the cases in various forms. These, however, can be associated, or follow one another, in the same subject. Nevertheless there seems to be some opposition between the paralytic and heart forms, whether the pathogenic mechanism presents some differences or the enforced rest due to paralysis protects the heart.

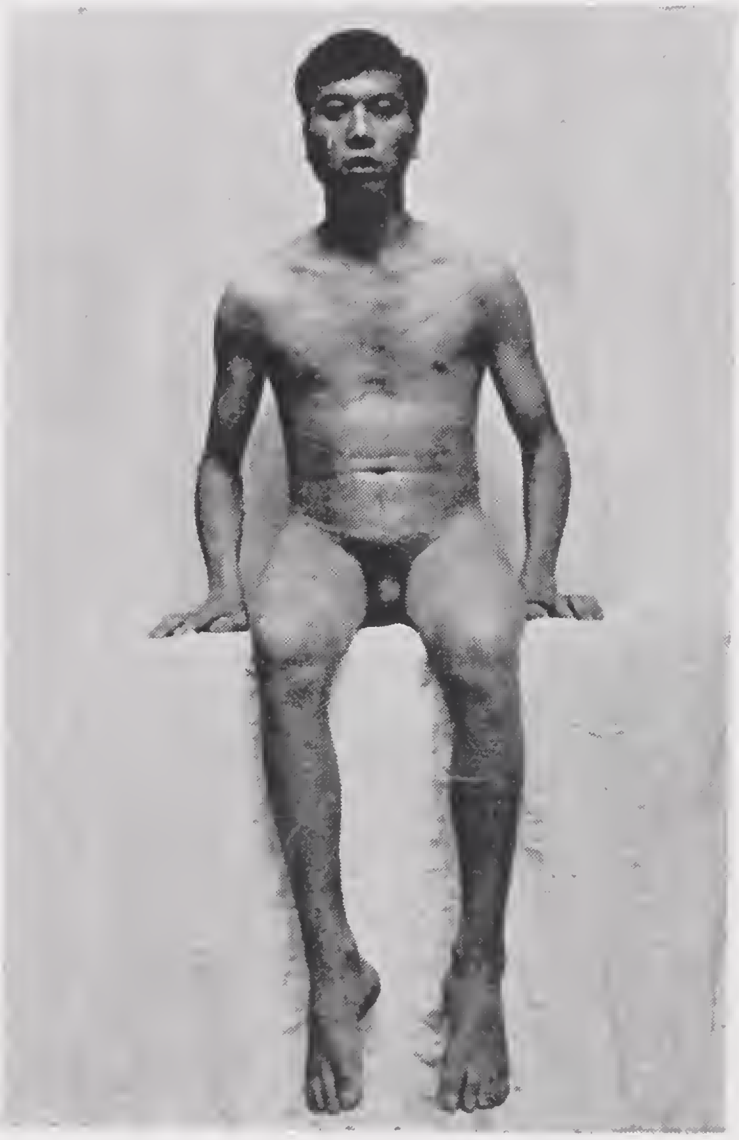

Fig. 90. Beriberi: Dropping Foot Symptom
Courtesy Dr. E. P. Snijders, Indisch Instituut, Amsterdam

1. *Concealed forms:* They are very frequent in time of "epidemics" and are the result of incomplete avitaminosis. Diagnosis is clinically difficult. The practical importance is considerable because from lack of precautions serious cardiac symptoms can appear either in the subject himself (sudden death with its medico-legal problem) or in the infant nursed by a mother of unsettled dietetic balance.

Here vague symptoms predominate: dyspepsia, constipation, lassitude, slight neuritic troubles, fast and slightly jumpy pulse, shortness of breath, slight anemia, no fever, no albuminuria.

2. *Dry beriberi or atrophic beriberi.* This is the picture of a neuritis striking mainly the lower limbs, more rarely the arms (radial nerve), and

exceptionally the nerves of the head (except, perhaps, the pneumogastric nerve).

The onset is insidious: slight tibial edema, painful, straggling walk, difficulty in squatting and standing up again (paresis of the femoral quadriceps), loss of perception of the diapason (toes, then tibia).

The symptomatology then completes itself, the deficit being mainly on the side of motivity: paresis, paralysis, frequency of dropping foot, possibility of radial drop of the hand, tendinous areflexia, muscular atrophy, alteration of electrical reactions.

On the side of feeling, one observes paresthesia and hypoesthesia. The muscles are painful when pressed. The recurrent and phrenic nerves are sometimes afflicted with vocal or respiratory troubles. Intelligence is intact. Heart troubles are often noticed but they are slight: tachycardia, slight dilatation of the heart.

Nervous lesions can be irreversible (lesions of the neurones) and definitive infirmity subsists with sometimes consecutive retractions.

Serious ocular lesions are reported: edema of the papilla, retinal hemorrhage, ophthalmoplegia.*

3. *Wet, hydropic, cardiac beriberi.* As we have said, neuritic phenomena are in these cases often discreet or nul, or appear only later on. In the earlier stages, cardiac beriberi presents nothing but a fast, labile pulse, shortening of the breath, palpitations with more or less edema.

At a more advanced state the symptoms become more serious: precardial pains, intense palpitations, heaviness and epigastric pains, dyspnea, orthopnea. The edema is more marked.

The shock point widens and one notices epigastric palpitations. The heart has increased in volume, especially the right heart and the conus arteriosus. The heart sounds are normal except when secondary deficiency appears.

The electrocardiogram shows abnormalities, particularly a predominance of the right ventricle and shortening of the P-R interval. The maximum arterial pressure is about normal, the diastolic pressure being low. Hence jumpy pulsations are easily audible arterial souffle. Venous pressure is increased.

Painful hepatomegaly, oliguria, edema, and extravasations appear. Hypoproteinemia may possibly interfere here.

At the extreme, even with symptoms of cardiac failure (but much more serious), appears fulminant beriberi, "shoshin" of the Japanese. The shoshin can be fatal for the afflicted within twenty-four hours or even more suddenly, in which case, if the subject has so far appeared to be in a satisfactory state of health, a medico-legal problem may have to be faced.

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* Recently the encephalitic syndrome of Wernicke has been attributed to an avitaminosis B_1. The study was made on European prisoners of war in Singapore who had been debilitated by a persistent diarrhea. Besides the gastrointestinal disturbances, the following symptoms were observed: ocular troubles, nystagmus, apathia, insomnia, amnesia, orientation troubles, semi-coma or coma, ocular paralyses. Hemorrhages were seen microscopically in the mamillary bodies (De Wardener ans Lennox, 1947).

Cardiac beriberi is also exempt of fever and usually of albuminuria (except in marked renal stasis).

Infantile beriberi: Appears among infants nursed by mothers either ill or apparently healthy. This form is exclusively cardiac and of obscure symptomatology. Sometimes the evolution is very acute and soon fatal: constipation, pallor, vomiting, screams, muscular stiffness, cyanosis, convulsions; the vomiting may be associated with signs of hyposystole and of edema. Hypertrophy of the heart is notable.

PROGNOSIS

The prognosis of cardiac beriberi is very severe, if it is not correctly treated. Infantile beriberi is particularily dangerous. Paralytic beriberi is less serious from the vital point of view but it sometimes creates irreversible lesions and permanent infirmities. Concealed beriberi is not without danger (asystole).

DIAGNOSIS

It can be difficult in concealed cases and could be simulated. Inquiries about the diet, tendonous areflexia, lability of the pulse, the squatting test can guide the clinician. Research in the blood and urine can be made by the biochemist.

In cases of epidemic, diagnosis becomes easier, especially when associated with the inquest concerning the diet.

When pronounced, cases of sporadic beriberi lead to confusion: the nervous form with neuritis of chemical origin (phosphate of orthocresyl, lead, etc.), particularly with alcoholic neuritis. In fact, the latter is really related to lack of thiamin (alimentary deficiency, defective resorption, increased needs for the metabolization of alcohol).

The edematous form may be confused with nephrosis (albuminuria), cachectic edema (ankylostomiasis), and commonly deficiency edema which seems, moreover, to be frequent in cases of beriberi.

Beriberic cardiopathy may make one consider various asystolias: mitral deficiency, circulatory troubles, particularly alcoholic myocardosis. The latter again is related to lack of thiamin and brings an etiologic diagnosis where the inquiry will be decisive (if necessary, analysis of the blood for alcohol).

It seems that circulatory disorders in relation to deficiency where the lack of thiamin plays an important but not unique part are rather frequent even in a civilized environment and can take various clinical aspects (Weis and Wilkins in Boston). This is a transitional zone where classic beriberi represents an advanced stage.

Beriberi cardiac disorder is notably aggravated by injection of adrenalin. The mechanism of this test, known as Alsmeer's test, is attributed to a paradoxal action of adrenalin, possibly in relation with the acidity of the tissues, which leads to the wider dilatation of the arterioles and which encumbers the right heart more seriously. It should be attempted only with great precaution because of the clinical aggravation it may bring about. One will notice, for instance, an increase in venous pressure with a drop in diastolic pressure.

TREATMENT

Complete rest, elimination of deficient farinaceous food from the diet, total reduction of glucids are imperative. If the state of the alimentary canal allows it, food rich in thiamin should be utilized: Phaseolus radiatus of Indonesia, slightly sifted flour, oats, arachids, soya, egg yolks, various vegetables (white cabbage, Brussels sprouts, spinach), liver, kidneys.

Preparations from bran-extract (tike-tike from the Philippines, Dedek from Indonesia) can be prescribed as well as nonautoclavated yeast. One will use preparations of pure thiamin in large doses, and in urgent cases intravenously. The venous introduction of 100 mg. does not bring about any illness, but it is not necessary to give more than a half or a third of this dose. Heart cases may respond rapidly to pure thiamin. It is always necessary to use several vitamins in association (B_2, PP).

Against circulatory manifestations, digitalis is of little use (Wenckebach), adrenalin dangerous; pitressin, on the other hand, is favorable as well as strychnine. Morphia has its usual indications. Bleeding is advisable in case of heavy venous congestion.

Nervous lesions do not respond so well to vitaminic treatment. Symptomatic treatment should be associated with it: electrotherapy, massage, and avoidance of deformations by appropriated orthopedic measures.

PROPHYLAXIS

Polished rice and white flour as staple food are to be avoided. Belgium's experience, for example, during the period 1940–1945, has shown the value of bread, if not complete, at least sifted only to 85 per cent. According to Brull, the proteic ration is also increased by this method, and even a portion (not to be neglected) of cellulose is used.

(b) VITAMIN B_1, RIBOFLAVIN, LACTOFLAVIN

This substance is most common in all vegetal or animal cells in the form of a phosphoric ester which is the co-ferment of various enzymes, in particular of the yellow ferment of Warburg and Christian and, therefore, in action in general metabolism. Furthermore it probably plays a part in vision.

The substance is not very soluble and has a good heat resistance (100 C. in acid surroundings); it is not altered by oxygen but by light.

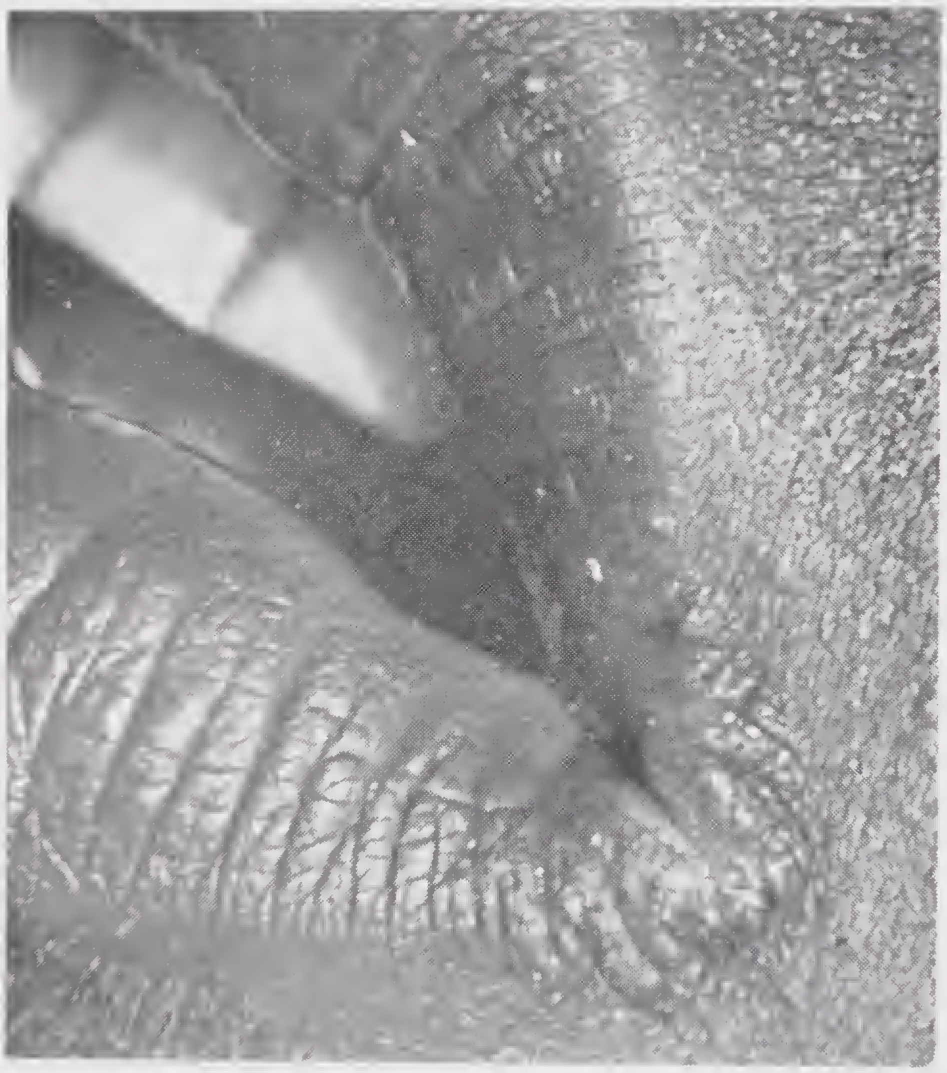

FIG. 91. ANGULAR STOMATITIS

Erosion in the angle of the mouth with elevated borders. Malay boy, 12 years (Courtesy Dr. P. Fascal)

Riboflavin $C_{17}H_{20}N_4O_6$ is a combination of iso-alloxin with a molecule of d-ribose. It presents itself in reddish crystals giving, with water, a fluorescent greenish solution (0.25 per thousand).

Brewery yeast, pig liver are especially rich, i.e., 10 to 100 mg./Kg. for the first, 30 to 35 for the second. Human serum contains 25 γ/Kg.

Pathogenesis: The daily need might be of 1 to 3 mg. Signs of deficiency in B_2 are: Cheilosis or cheilitis, marginal and mainly angular (syndrome of perleche), a state of seborrheic irritation of the naso-labial canals, angular blepharitis, desquamation of the scrotum, magenta tongue, visual troubles, and finally, photophobia, conjunctivo-corneal vascularization. Among young rats, it interferes with growth. Perhaps it is a cause of steatorrhea.

Treatment: It is prescribed in cases of beriberi, pellagra, sprue, and coeliac diseases at a rate of a few milligrams a day (up to 10).

(c) PP VITAMINS OR ANTIPELLAGROUS, NICOTYLAMID, NIACIN

It is the most thermostable part of Group B, persisting in extract of autoclavated yeast.

Chemical properties: This vitamin is amid of pyridin-3-carbonic acid. It appears as colorless crystals, soluble and very stable in heat. The acid is a pro-vitamin.

Repartition in nature: It is widely distributed, in particular in yeast (60 mg./Kg.), meat (40–50 mg./Kg.), kidneys (63–83) liver (120). Human serum contains 7–9 mg./Kg.

Physiologic action: Nicotylamid after phosphorylation is a constituent of various co-ferments. It intervenes in the general metabolism of the glucids (alcohols and acids) as acceptor of hydrogen (H_2 being fixed on the N and the CH next). The needs of man would be 50 mg. a day.

Experimental animals: A deficient dog presents the "black-tongue" disease. Nicotylamid is a growth factor for several bacteria.

Deficiency indications: pellagra, sprue, erythrodemis, edema of Quincke, estival hydroa, porphyrinuria, drug intoxications and chilblains.

In pathology, PP vitamin is responsible for most of the symptoms of pellagra, where complex hydrosoluble deficiencies are, however, frequent. The relation with porphyrinuria is uncertain.

Pellagra

GEOGRAPHIC DISTRIBUTION

It is extremely varied and formerly reached even Western Europe (France) where it is actually sporadic (misery, psychopathy). The very term "Pellagra" is Italian and refers to cutaneous irritation. It is still rather frequent in the Balkans, Spain, Egypt, Caucasus, India, the South of the United States of America. In Central Africa, it is probably rather widespread but we lack typical descriptions.

ETIOLOGY

Primary pellagra is linked to a monotonous diet, where certain farinaceous foods predominate, especially maize. The other B vitamins are also missing at the same time. Secondary pellagrous states have been observed in cases of enteritis and among alcoholics. Clinical manifestations in countries of temperate climate mainly take place in springtime or at the beginning of summer (influence of light).

PATHOLOGY

It is not very instructive, showing but few extra details over the clinic: emaciation, glosso-stomatitis, digestive ulcerations. However, one must note lesions of the central nervous system (demyelinization of the posterior and lateral strings of the medulla, alteration of the cortical and nuclear neurones) and of the peripheral nerves, neuritis reminiscent of the neuritis of beriberi, if not identical to it). On the skin, one notices inflammation followed by atrophy with pigmentary alteration.

SYMPTOMATOLOGY

Evolution, just as that of most of the avitaminoses, is very chronic and

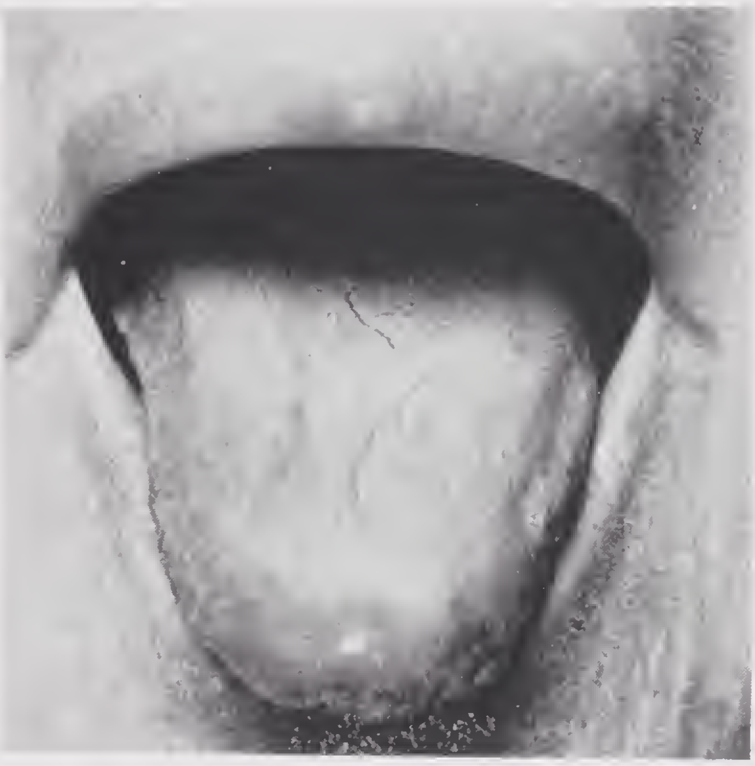

FIG. 92. PELLAGRA TONGUE
Showing atrophy at tip and margins (courtesy Dr. J. M. Ruffin)

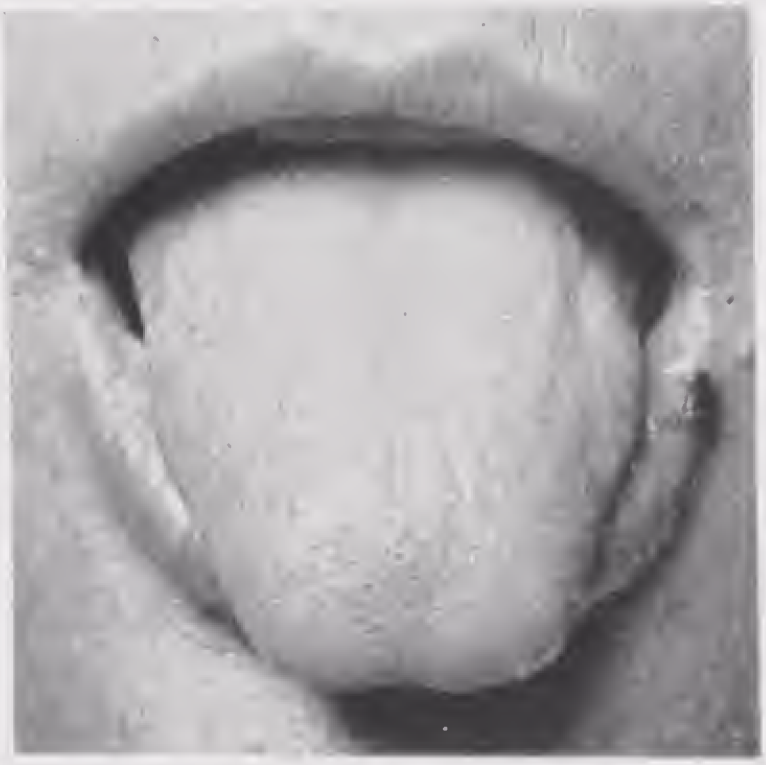

FIG. 93. NORMAL TONGUE
Represented for comparison (courtesy Dr. J. M. Ruffin)

the beginning is insidious: tiredness, depression, lack of appetite, diarrhea, burning sensation in the extremities, etc. When the symptoms appear clearly, one observes a triad very characteristic but rarely complete on a given subject.

1. Erythema of uncovered parts, followed by keratosis, desquamation, pigmentation and, finally, atrophy. This erythema has a tendency to disappear in winter and reappear in the spring. The part of porphyrin as a photosensitizing substance explains, according to some, this seasonal variation. The "crazy pavement skin" observed on the buttocks, on the back, on the lower part of the legs, etc., appears in pellagra, mainly the infantile form.

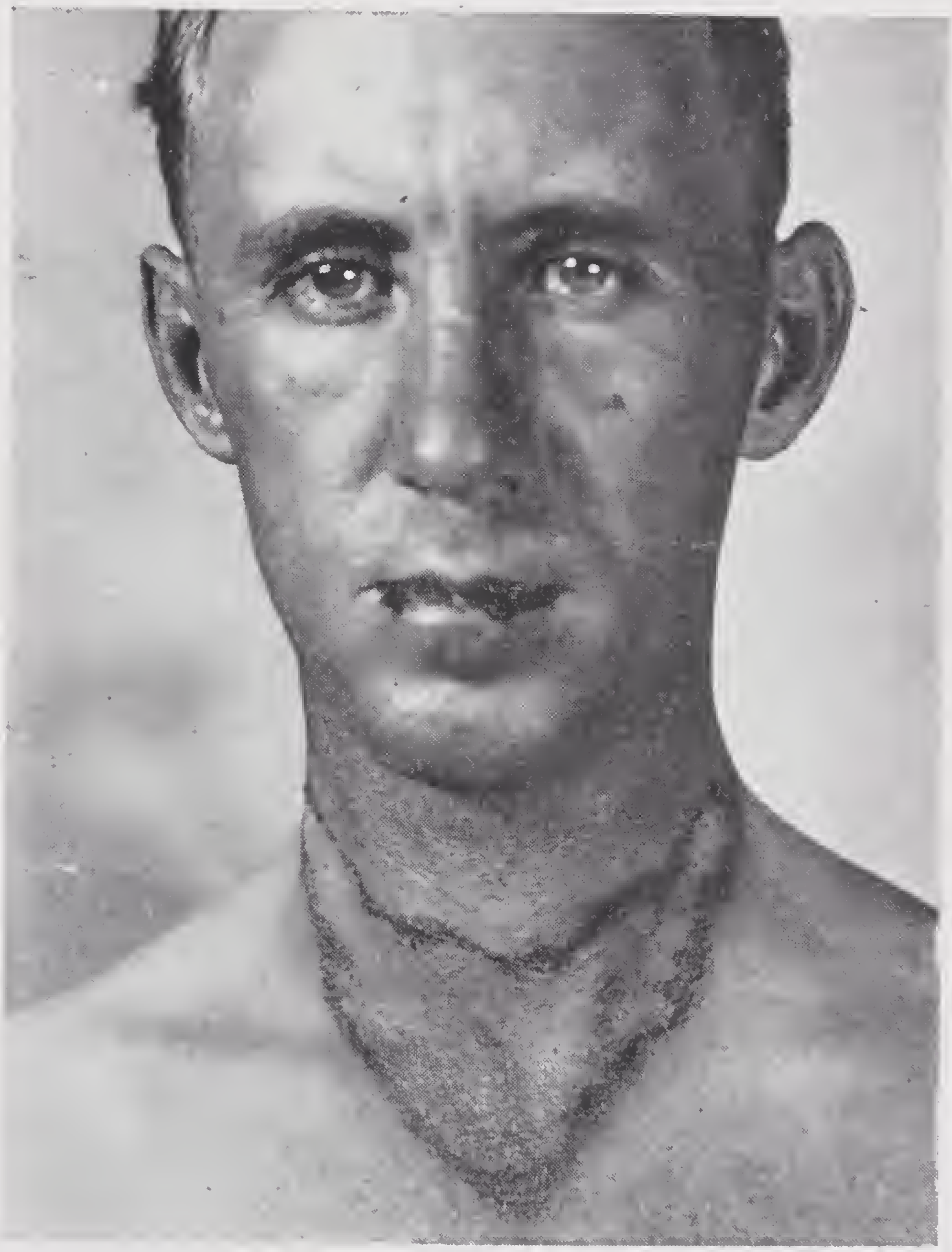

Fig. 94. Pellagra: Typical Collar
(Courtesy Dr. J. M. Ruffin)

2. Digestive troubles: Stomatitis, desquamative glossitis and sometimes even ulcerous, frequency of perleche (B_2), dyspepsia often with pyrosis, diarrhea, peri-anal erosions.

Blood shows moderate or pronounced anemia, hypochromia most of the time. Gastric achlorhydria is rather frequent even after histamine injections.

3. Neuro-psychic troubles. Nervous signs can vary to a considerable degree, as can the localization of lesions.

On the side of sensitivity, one observes paresthesia, burning pains ("burning foot," hyperhydrosis). Headache is common.

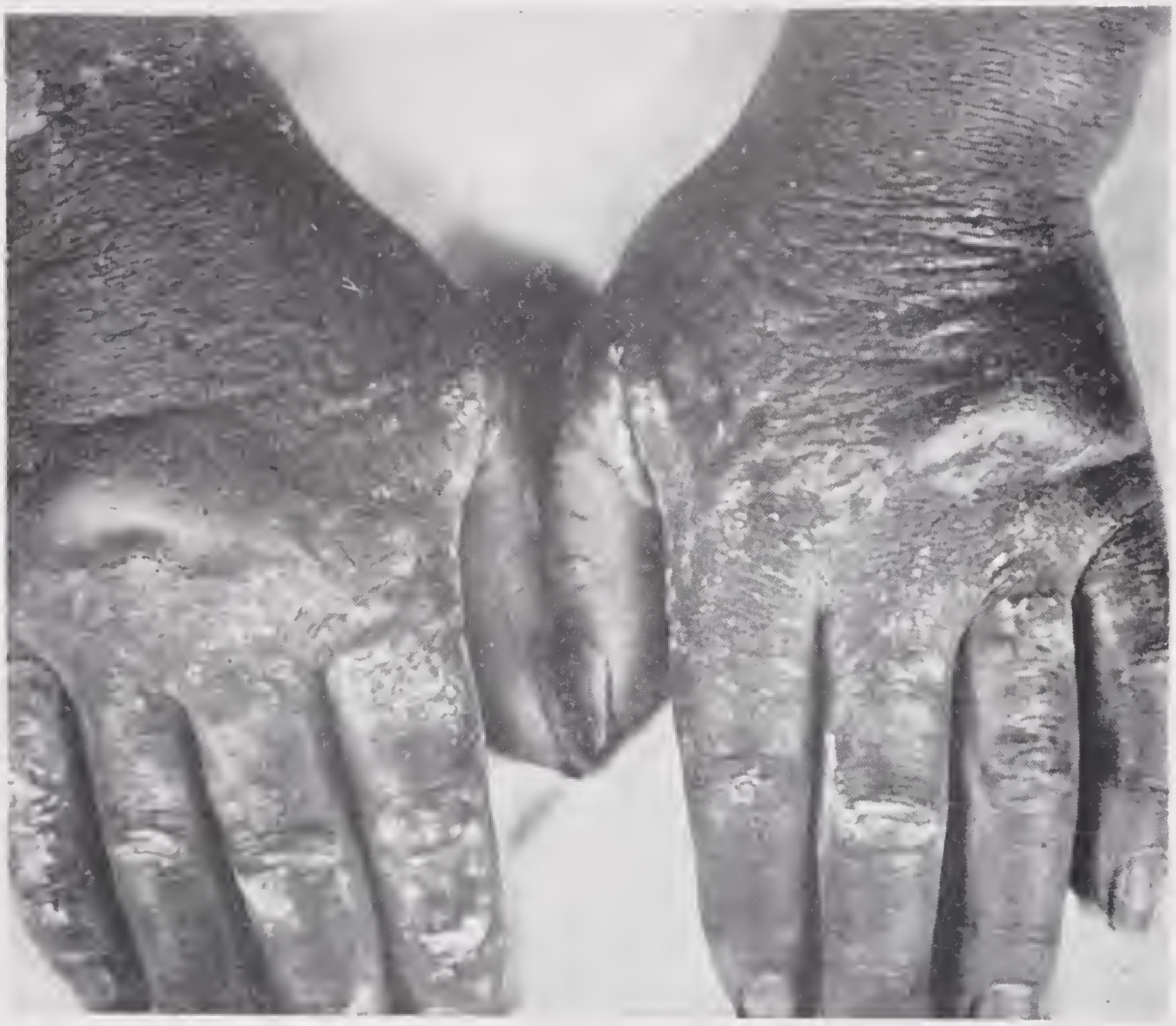

Fig. 95. Pellagra
So-called wet type with bullous lesions (courtesy Dr. F. C. Combes)

Motor symptoms commonly include spasticity (paraplegia), trembling, contracture. Epileptic fits are observed.

Psychic troubles are generally of a depressive nature: mutism, hypochondria, persecution mania. Manic agitation is rarer. Suicide can follow deep melancholy or madness. Confinement is often necessary.

Prognosis: Old cases, especially those with psychic disorders, have a severe prognosis.

Diagnosis: It is only easy in typical cases particularly where the characteristic symmetrical erythema of the extremities, neck, face, etc., exists. It reminds one, on the whole, of solar erythema. Discovery of marginal lesions in the tongue is also important.

TREATMENT AND PROPHYLAXIS

A well balanced diet with vegetables and particularly meat or fish gives a perfect protection against the disease. Whole bread also has a real value. During German occupation of various European countries in the recent World War, pellagra was not reported among undernourished subjects who had "hunger edema" (see further).

Treatment is essentially dietetic: proteins, especially animal, vegetables and fruit (other hydrosoluble factors).

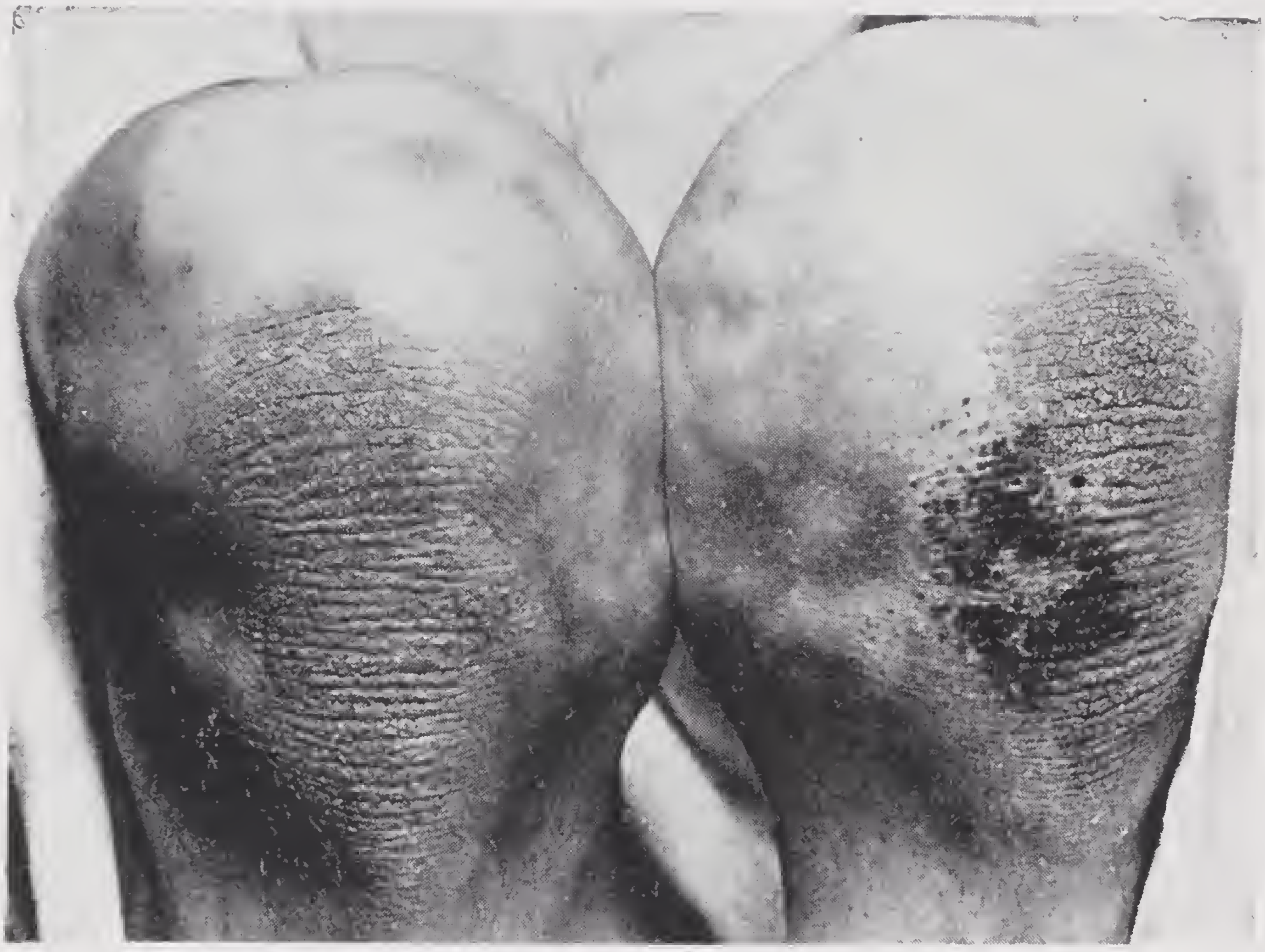

Fig. 96. Pellagra
Symmetric manifestations on the knees (courtesy Dr. J. M. Ruffin)

As medication: yeast extract (Marmite).

Nicotylamid (3 or 4 times, 100 mg. per os). Other vitamins of group B should be given because of the associated deficiencies. One can also use the acid and its salts, but they give vasomotor-cutaneous reactions (redness, urticaria).

Syndrome of Depigmentation, Edema, Anemia

A symptomatic complex has been described as occurring in different places in Africa and in Indo China, sometimes under native names (Bwaki in the Belgian Congo, Kwashiorkor on the Gold Coast), sometimes under the above-mentioned one or even as "malignant malnutrition" (Trowell).

The complex includes anemia, loss of weight, diarrhea and even steatorrhea, general depigmentation of the teguments and hair (Bwaki), in connection possibly with pantothenic acid, desquamation and epidermic exfoliation at the extension side of the limbs, "crazy pavement skin,"* peribuccal, nasal, peri-anal, scrotal excoriations, glossitis and cheilosis, angular stomatitis (B_2), edema, hypoproteinemia especially of the albumins, myocardosis, bradycardia, muscular weakness, lethargy, anorexia, dehydration, oliguria, fatty degeneration of the liver (Gillman) and anomalies of the intestinal motility seen in the x-rays.

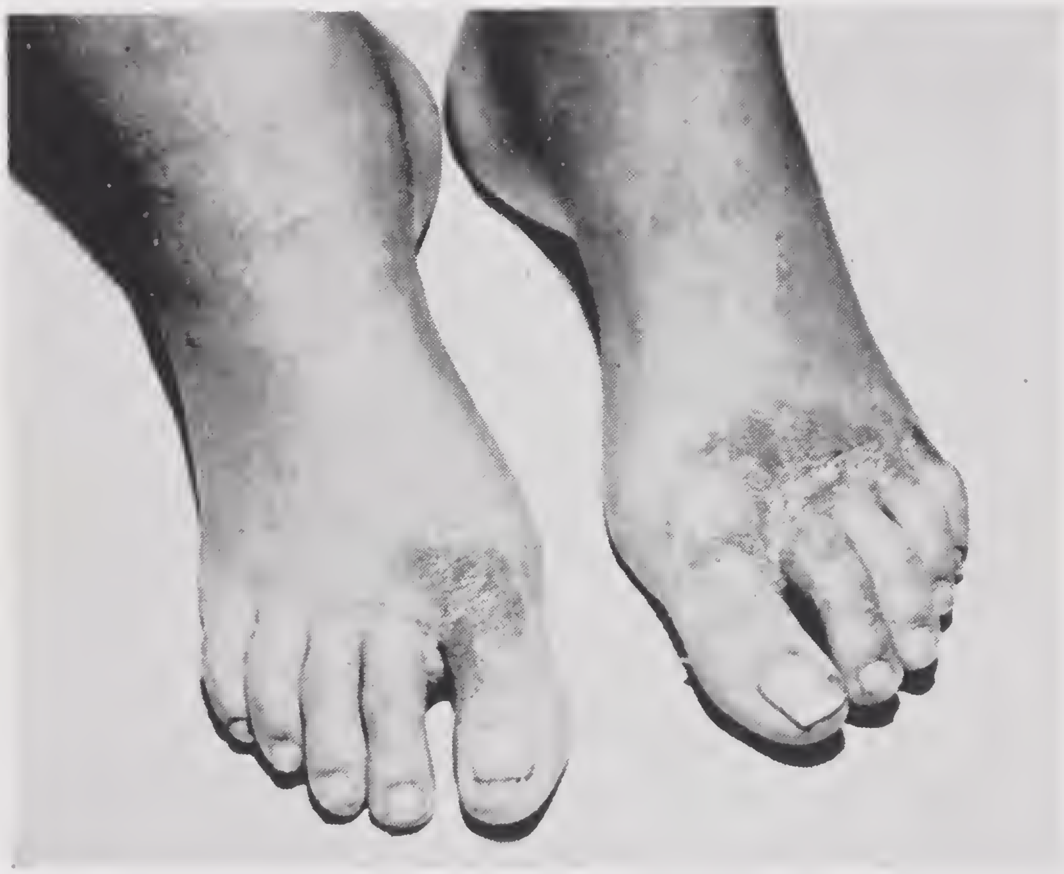

FIG. 97. PELLAGRA: SYMMETRIC LESIONS ON THE FEET
Army Institute of Pathology. Neg. No. D45456. P-9. No. 1. Washington 25. D. C.

The poor populations, and especially the abandoned children among them, are hardest hit by this disease. It is of common occurrence at the end of the dry season when the food supplies are low. The disease seems to be due to very complex deficiencies, with a strong pellagric component, deficiencies of Group B, and a hunger edema factor. Helminthiases are often associated with it. Hyposideremia has been incriminated (Pieraerts). The prognosis is severe.

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* According to Trowell (1940) the common mosaic skin must be distinguished from the "crazy pavement skin": "The crazy pavement skin starts as jet-black patches on the skin of the buttocks and the pressure areas of the back and the irritation areas of the perineum. They look as though dull black paint had been printed on to the skin, had dried and had cracked and was starting to peel off. Desquamation occurs early and reveals pale, even dead white underlying skin. Ulceration easily occurs."

The treatment requires good alimentary hygiene and administration of vitamins and animal proteins. Ventriculine associated with chlorhydric acid has been found of use.

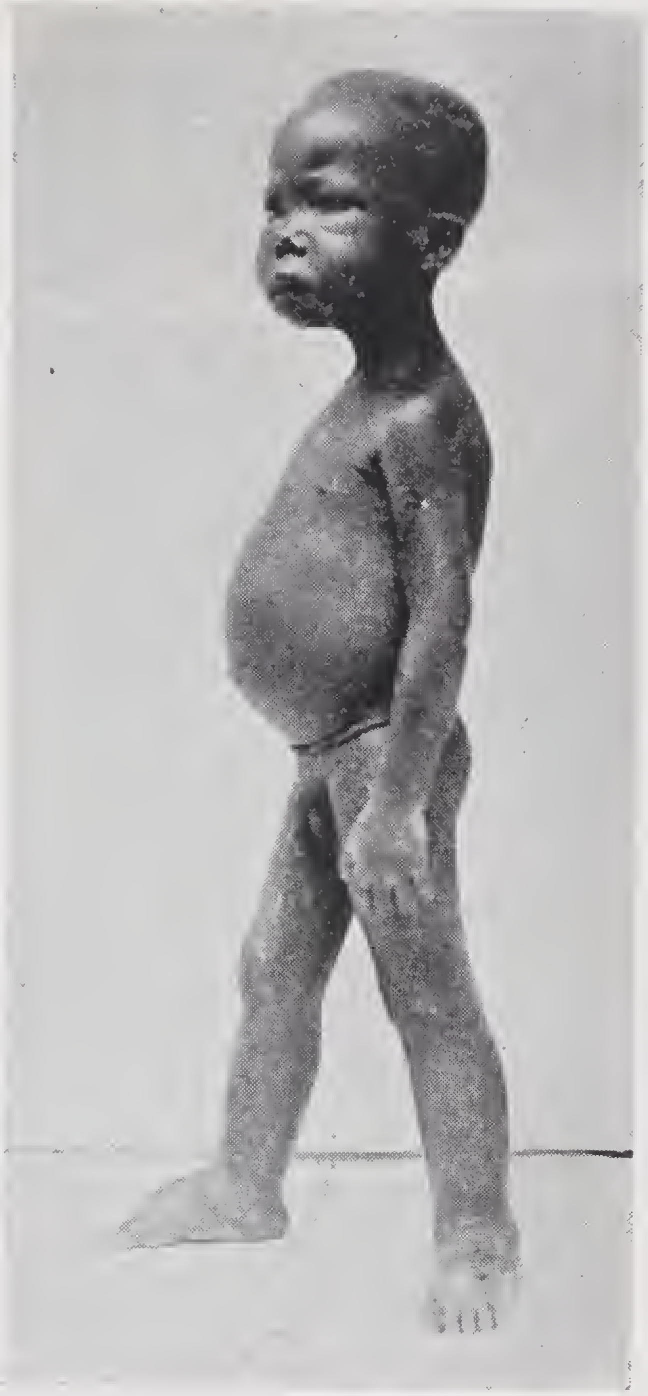

FIG. 98. MALNUTRITION AND EDEMA IN CONGO CHILD
Coll. Tropical Institute, Antwerp

(d) OTHER B VITAMINS

Pyridoxin, adermin, B_6, derived from pyridin, is a crystalline, colorless substance, soluble in water, rather widely spread (germ of corn, skin of rice, brewery-yeast, soya, yolks of eggs, liver, fish, etc.), the physiologic part of which is, however, imperfectly known as yet.* Adermin is the chlorhydrate of pyridoxin. Among rats this factor cures dermatites of pellagrous aspect.

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*Pyridoxine, as an aldehydic derivate (pyridoxal) esterified by phosphoric acid, is the co-ferment of a decarboxylase indispensable for the metabolism of amino-acids (Abderhalden, 1947) which are transformed into amins with liberation of CO_2. In its absence, xanthurenic acid (carbonic dioxyquinoleine) appears in the urine of several animals. This disturbance in the metabolism of the amino-acids explains the variety of symptoms: disturbance of the iron metabolism, microcytic hypochromic anemia, alteration of the nervous system, etc.

The daily needs of the adult, not well established, might be of 2 to 3 mg. This is, at least, what a normal diet provides.

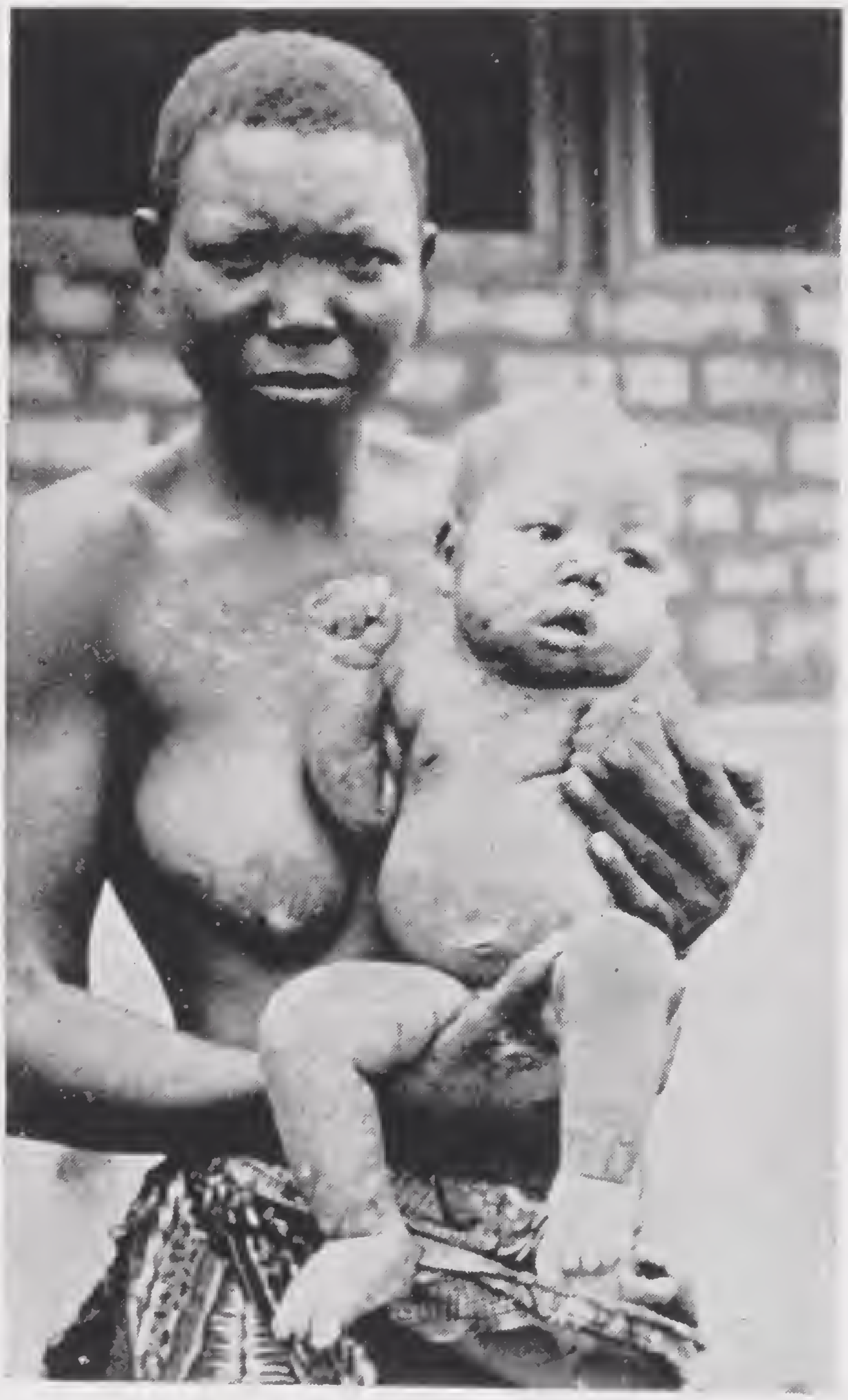

FIG. 99. DEPIGMENTATION-EDEMA-ANEMIA SYNDROME IN THE CONGO
Phot. A. Fain, Tropical Institute, Antwerp

Therapeutic indications are somewhat uncertain: neuro-muscular troubles, pseudo-hypertrophic muscular dystrophy, possibly the nervous symptoms of pellagra where it is prudent to prescribe it (20 mg., three times a day).

Pantothenic acid: Filtrating factor of the thermostable fraction of the vitamin B: $C_9H_{17}O_5N$ or Dioxy-dimethyl-butyrylalanid, is widely spread but in small quantities in plants and animals (battitures of rice, arachid, yolk of eggs, kidney, potatoes). It is a factor of bacterial growth. The physiologic role is not well established: regulating action, especially of metabolism, toward epitheliums and hair. The need might be of 10 to 50 mg. The blood contains 190 to 320 γ per liter.

Pathologically, animals also show cutaneous troubles: dermatitis of the chicken, alteration of the coat in rats, foxes.

For man, therapeutic indications are still vague: infectious hepatitis, respiratory or digestive catarrhs, diseases of the hair (syndrome of discoloration?)

Dosis: 50 to 100 mg. a day.

Folic acid: 6-oxy-2-amino-pteridine, p-acid aminobenzoic-ac-glutamic. This product seems to be of fundamental importance in treatment of macrocytic anemia of various origins: sprue, pernicious anemia, and megaloblastic anemia of the suckling. On the contrary, the product is inactive in cases of secondary anemia, hypochromic anemia, leukemias, and aplastic anemia.

In the rat Bartonellosis, folic acid is curative and protective. Its action should be tried in human Bartonellosis.

Dosis: 20 mg. per day of the synthetic product.

Folic acid (the name is derived from its presence in green leaves) is an acid nitrogen substance derived from xanthopterin and containing a p-aminobenzoic and a glutamic acid chain. It is found normally in hepatic extracts.

Folic acid is widespread: in leaves, yeast, germinating seed, liver, kidney.

Hunger Edema

This syndrome is not tropical but can complicate various states of deficiency: beriberi, pellagra, syndrome of depigmentation, epidemic dropsy.

ETIOLOGY AND PATHOGENESIS

In 1914–1918 in Germany and in 1940–1944 in Belgium, the affection appeared in the same conditions: semi-starvation, scarcity of proteins. The ration of sick people in Belgium was about 1,300 calories with less than 25 Gm. of proteins. Experimentally such a condition can be produced in the dog with the same diet.

This alimentation brings about hypoproteinemia with rarefaction of albumins particularly, therefore lowering the osmotic tension of the plasma. A diminution of the efficacy of the myocard is also found, and eventually overwork. The part of avitaminosis seems nul. The edematogenous limit is 5.5 per cent of the total plasmatic proteins and 2.5 per cent of albumins.

SYMPTOMATOLOGY

Progressive onset, loss of weight, asthenia then edema, especially in the declivous parts, are the revealing symptoms. Polyuria, at least nocturnal, is pronounced. The pulse is slow, the tension low, the electro-cardiogram is subvoltated. Nervous signs are nul or not very clear. The blood, not anemic, is poor in protein (3 to 4 per cent instead of 7 to 8) especially in serines. Basic metabolism is lowered which is, however, frequent in case of starvation.

The evolution is rather favorable, notwithstanding that deaths in hypoglycemic coma and hypothermy have been noted (Belgian prisons during the war).

Diagnosis will be based on the history; significant also are: exclusion of cardiac, or renal lesions, bradycardia, polyuria with absence of albuminuria, absence of signs of cardiac decompensation.

Treatment: Complete rest and a richer diet with a sufficient amount of proteins have shown striking improvement.

Epidemic Dropsy

Definition: Syndrome observed in India and closely related with an intoxication by the Argemone Mexicana essence: edema related to cutaneous and digestive phenomena is found.

Geographic Distribution: The disease is known only in Bengal and neighboring provinces. There have been occasional cases in Indians emigrating to other countries.

Etiology: Since the works of Lal and colleagues, the disease has been attributed to intoxication by Argemone essence which is found in certain essences of mustard. This is utilized very extensively in Indian cooking (30 Gm. per capita per day). Argemone is a weed which contaminates the mustard harvest. The predominant use of rice contributes, it seems, in the production of the disease.

Pathogenesis: The poison is supposed to be the cause of vascular dilatations, sometimes of the skin, sometimes of the heart, etc.

Symptomatology: The rather variable onset includes fever, digestive disorders and a seemingly toxi-infectious period. Subsequently cardiac disorders appear: dilation of the heart, tachyarythmia, dyspnea. Sudden death has been noted. Edema generally limited to the lower limbs has given the name to the disease. The condition of the skin shows erythema, petechiae, or vascular nodules which bleed easily. The condition of the reflexes varies. Glaucoma is frequent.

Prognosis: Reserved.

Diagnosis: Dry beriberi with its slow evolution, its paralysis and atrophies, offers no problem for the differential diagnosis. Wet beriberi is more confusing. The toxi-infectious period, however, is missing here, and also the definite gastrointestinal disorders, and especially the skin manifestations. The action of thiamin on the beriberi heart may be of assistance in the diagnosis.

Treatment and Prophylaxis: The admitted etiologic concept sufficiently indicates their nature. Good care and attention permit the production of mustard grains only. Rice must not be used. Good food and rest are essential.

B. VITAMIN C OR ANTISCORBUTIC

Physicochemical characteristics: $C_6H_8O_6$ or l-ascorbic acid is the lactone of an acid corresponding to a hexose. It can present itself reversibly in reduced form or in oxidated form (by taking or losing 2H). Colorless crystals, highly soluble in water, giving a very acid and dextrogyral solution, reducing the Fehling, changing methylene blue into a leuco-derivate. A more pronounced oxidation destroys the vitamin. Heat easily alters it. Away from air and in acid solution it can, however, bear 100 C. Among plants there exists a nonoxidizable ascorbigenous substance.

Physiologic action: Ascorbic acid seems to be a carrier of hydrogen. It helps the formation of bones and teeth and increases the resistance of the organism (fatigue, infections, toxins). Man needs about 50 mg. per day and even more.

Experimental animal: Guinea pigs fed only on cereals soon develop fatal scurvy. Most animals synthesize vitamin C.

Distribution in nature and prophylaxis: No vitamin is more widely spread nor more abundant ($^1/_2$ Gm. to 2 Gm. per Kg. in various vegetables): the citrus fruits (50–100 Gm. cover man's needs), cabbage (100 Gm.), horseradish (50 Gm.), potatoes (500 Gm.), cress (100 Gm.). Paprika (capsicum), dog rose (Cynorrhodon) contains several Gm. per Kg.

Meat is rather poor (20 mg./Kg.) but the suprarenal glands are very rich (2 Gm./Kg.), milk is fairly rich (10–100 mg./Kg.). Human serum contains 5 to 10 mg./Kg. Eggs and honey have none.

*Scurvy**

Definition: C avitaminosis, characterized by fragility of the capillaries, hemorrhages, gingivitis, and anemia.

HISTORY

Two or three centuries before the discovery of vitamin C, observation had linked to the lack of fresh food an affection which mainly victimized sailors, besieged people, etc. Even in those days the preventive use of lemon juice was known in the British Navy. In 1747, Lend experimentally confirmed its value.

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* French: scorbut; German: skorbut.

GEOGRAPHIC DISTRIBUTION

The disease is as cosmopolitan as the abnormal diet which leads to it. For obvious reasons it is more frequent in the polar regions, at least among travelers. Eskimos know through experience the use of raw meat, blood, viscera, and even the gastric contents of the seals, etc., in avoiding scurvy.

In the tropics, unbelievable as it may seem, the disease has been noted among rationed or rather badly rationed subjects.

ETIOLOGY

The observation of centuries, experimental trials, or trials made under almost experimental conditions during polar expeditions, etc., show the protective part played by fresh food. Fresh meat (seal, bear, etc.) was sufficient to protect several exploratory expeditions. During the siege of Kut el Amara British soldiers who ate their horses avoided the scurvy which struck Indians subsisting on a vegetarian diet. The latter, however, eating whole wheat, escaped the beriberi which struck Europeans eating white flour.

Experimentation on guinea pigs (Holst) has precised these facts. It should be noted that although vitamin C is common, especially in a large number of vegetables, it is also a very alterable vitamin. Oxidation destroys it rather easily. Not too prolonged cooking leaves more or less of the vitamin intact, but one must also take into consideration the aqueous extraction which in certain culinary preparations is thrown away. The canned food industry presents the same problem. The time of "whitening" (cleansing) of the vegetables previous to sterilization is perhaps more dangerous than the latter. Canned food of this type generally contains a certain amount of vitamin C.

Conservation of vegetables in refrigerators also greatly diminishes their value: cabbages preserved at normal temperature lose 30 per cent of their C factor in six weeks. Around 1 C. this loss is still 25 per cent. Potatoes, in the course of preservation, lose approximately 50 per cent their activity.

The process of conservation, based on desiccation or autoclavation or even extreme cold, demands a short period either in boiling water or through steam to stop the process of fermentation, this operation being followed by cleansing in water. The loss of mineral salts and of vitamins is important during this operation.

After this treatment, deep freezing probably is the best method of conserving what is left of the vitamins. Desiccation makes vitamins A and C disappear through oxidation, and perhaps to a smaller degree vitamin B_1 also. The autoclave alters vitamin A (above 115 C.), vitamin C partly, and to a certain degree, vitamin B.

PATHOGENESIS, PATHOLOGY

Vitamin C has a part in the equilibrium of the tissues of support, including the vascular wall. Therefore, cutaneous subperiostial, intramuscular and intra-articular hemorrhages occur. The osseous tissue presents an abnormal disposition of the mineral elements, the alveolar processes of the maxillar bones are resorbed, teeth become altered. Anemia is constant.

In fact, vitamin C is an extremely general intermediary metabolic, and any tissue may suffer by its absence.

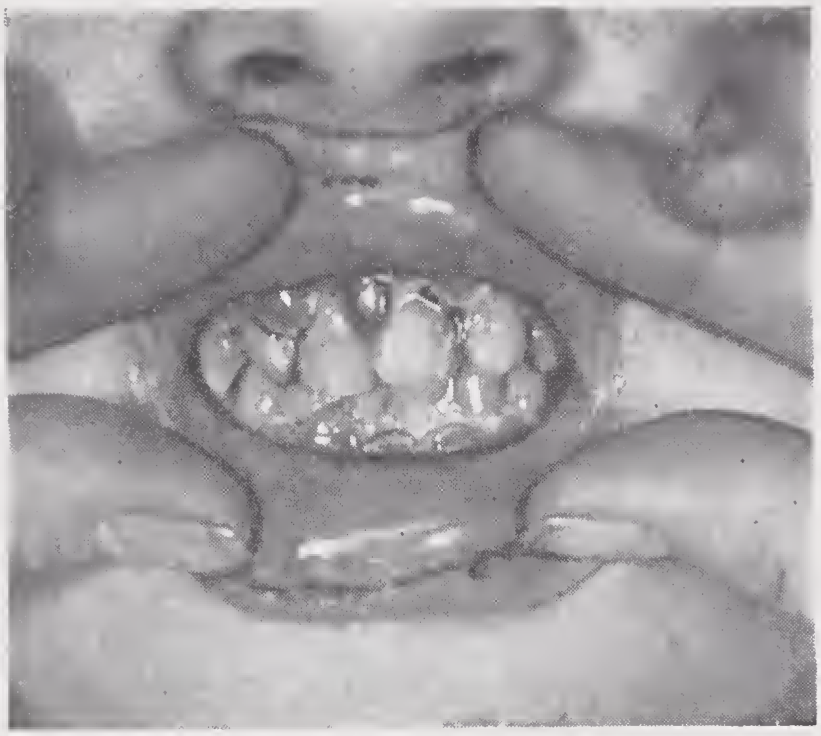

FIG. 100. SCURVY: SPONGY, BLEEDING GUMS
Courtesy Dr. E. Urbach, "Skin Diseases, Nutrition and Metabolism." New York, Grune & Stratton, 1946.

SYMPTOMATOLOGY

Incubation is very long (several months) and marked by increased fatigue, anemia, gums that bleed easily. This state can exist alone and is sometimes rather frequent at the end of the winter, even in civilized countries. German occupation in Belgium failed to demonstrate these facts very clearly but this is a country where cultivation of vegetables and fruits is at a high level.

If the deficiency is deep, the symptoms will be more pronounced:

1. About the skin, peripilar papulation of the "goose flesh" type around the hair, with small hemorrhages at the top of the papulae. Ecchymoses of varying size appear. Infection produces pustulae, boils, and ulcers.

2. Locomotor system: Hematomes harden the muscles and make them painful spontaneously and when pressed. They sometimes suppurate. Concerning the articulations, one observes hemorrhagic dilatations, articular or periarticular. These symptoms constitute the typical picture among children (Barlow's disease), in whom the gingiveous and cutaneous signs are absent.

3. On the gums, bleeding dilatations are observed as well as ulcerations. This is quite often a precocious sign. Anemia is noticeable and the tendency to infection is greater.

Evolution, Prognosis: This illness is very chronic; when fatal, various complications may be implicated. Through lack of observance of proper diet, the prognosis is serious, and, of course, varies according to degree of deficiency.

DIAGNOSIS

Symptomatic association: fatigue, gingivitis, rheumatoid pains, draw the attention. The presence of anemia, a tendency to ecchymosis, an inquiry about the diet, will reinforce the diagnostic position.

A test indicating vascular fragility has been proposed. Göttlin applies a string at the crease of the elbow. A cup of measured pressure is applied and the petechiae counted in comparison with a normal subject. This method can, of course, be used only with subjects with a light complexion.

The measurement of ascorbic acid in the blood or urine is possible, the physician himself being able to make the saturation test. A normal individual eliminates enough of this product to discolor the dichloro-phenol-indophenol either immediately or within three days, if he takes 50 mg. 6 times per day of pure ascorbic acid. (Hoffman-LaRoche furnishes tablets of the reactive and of ascorbic acid with all necessary details concerning quantities.)

TREATMENT

No particular difficulties are encountered in treatment. According to the appetite of the patient, recourse is made to fresh food: meat, vegetables, fruits. Fruits of the citrus variety are valuable owing to their great digestibility. They contain, of course, besides the ascorbic acid, other vitamins of the same group.

Ascorbic acid can be prescribed per os or in injections in doses varying between 150 and 500 mg.

Various symptomatic treatments must be prescribed (gingivitis, hematomes, ulcers, boils).

3. VARIOUS VITAMINS

Bios I: It has not been definitely established whether this product, isolated from the enigmatic complex Bios reported by Wildiers at the beginning of the century, has any significance for man.

It is the mesoinositol $C_6H_{12}O_6$ (with cyclic structure), and seems to be a vitamin for mice.

Bios II, vitamin H, Biotin, $C_{10}H_{16}O_3N_2S$, of which two isomeric varieties exist, is an antidermatitis factor for rats. Its action in man is not well known (eczema, seborrhea). Animal viscera, liver, and kidney are rather rich. An excess of white of eggs blocks the biotin and provokes a desquamative state of the human skin (antivitamin).

Vitamin P (for permeability). Citrin, was extracted from lemon, or from paprika, by Szent-Györgi in the form of yellowish crystals. In scorbutic guinea pigs, 1 mg. of Citrin per day would inhibit hemorrhagic manifestations but not the other scorbutic manifestations. The product is composed of glucosides where the aglucones are flavones. The active product could be the rutin of similar structure. Lemon juice has a therapeutic action more extended than pure ascorbic acid.

*Sprue**

Definition: Chronic disease characterized by diarrhea with greasy stools, glossitis, emaciation, anemia. Resorption of food and vitamins is seriously impaired.

Recent hematologic literature mentions somewhat varying, but associated, syndromes, all classified as "sprue." The following discussion deals with the classic form as we have observed it.

GEOGRAPHIC DISTRIBUTION

The disease has been studied mainly in the Far East, also in the Antilles (Puerto Rico). Strong remarks its relative rarity in Africa, in spite of a commonly deficient diet and of the frequency of dysentery.

Sprue nostras is observed in many civilized countries of Europe and the Americas. No abnormal frequency was reported during the War of 1940–45 in Europe.

ETIOLOGY

It is commonly a disease of middle age, more frequent among women than men, more frequent among Europeans than natives. The etiologic part of various intestinal infections is willingly admitted but does not appear to be indispensable.

Ashford formerly stated as a cause *Monilia psilosis,* a type of yeast which is indistinguishable from a parasite of thrush common among sick people. It is now considered more an effect than a cause.

Environment has sometimes been incriminated. Houses where one catches sprue are said to exist in India and the dry rot (dried rottenness of the beams, etc., through the action of termites, molds, etc.) could be involved. No confirmation has been given.

Sprue is not an illness of primary deficiency. One observes it in highly privileged social classes. But secondary deficiency, through anatomic or physiologic disorders of the intestine, is a probable factor. The same etiology is advanced for the coeliac illness, or syndrome of Gee-Herter which is the counterpart of sprue, in pediatrics. Incriminated also are lesions of the cortico-suprarenals, interfering with the phosphorylation previous to the resorption of the glucids. Among adults, one finds definite intestinal antecedents in 30 to 40 per cent of the cases.

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* In Dutch, Spruw means "aphthous disease."

PATHOLOGY

The autopsy is not particularly characteristic: emaciation, dryness of the tissues which are free from fat, atrophy of the viscera, particularly the liver, brown atrophy of the heart. One can observe glossitis as in vivo.

The small intestine appears thinned and dilated, in other parts with atrophied villosities. Certain authors tend to believe that the latter case is a postmortem manifestation. But Manson-Bahr reports that sigmodoscopy shows an atrophic state of the intestinal mucus. The same picture is found with gastroscopy. Also observed at the level of the intestine have been inflammatory infiltrates and even small ulcerations.

The intestinal physiology is greatly disturbed. In cases of coeliac disease one observes losses of 75 per cent of fats, 15 per cent of azote, 45 per cent of glucids, and 80 per cent of the water from the ration, instead of the usual losses of 7 to 9 per cent. The results are obvious:

1. Voluminous stools, pale (bile is reduced to leuko-derivates), acid, and foamy (fermentation of the glucids), very rich in fats, besides being widely separated, in opposition to the picture in pancreatic disorders.
2. Glycemia: low, flattened curve after the glycemia test.
3. Tendency to acidosis and hypocalcemia (bases and calcium lost under the form of soap), osteoporosis, rachitism, hypocalcemia, loss of vitamins.
4. Various vitaminic deficiencies: susceptibility to infections, pigmentations, rachitism, hypocalcemia, etc.

These disorders are most highly developed among children. Osteoporoses are missing among adults, according to various observers (Fairley).

SYMPTOMATOLOGY

The onset is ordinarily progressive. Diarrhea, first quite ordinary (often in the morning—alarm-clock stool), gradually becoming diarrhea with typical stools: flat, voluminous, pale, foamy, and acid.

In the forms where gastrointestinal symptoms predominate, dyspepsia is notable, achlorhydria is frequent but generally histamine makes the acid appear. Abdominal meteorism is marked, the liver atrophied and surrounded by dilated segments of the intestine shows a certain dullness. The number of stools generally remains small (6 to 7). Tiredness, emaciation are more and more manifest with a neurasthenic syndrome.

In other forms buccal symptoms predominate or are associated with the preceding ones. The tongue is painful ("burning tongue"), when ingesting alcohol or spices it becomes red, varnished, shows aphthae, crevices, and finally atrophy. Esophageal dysphagia can also be seen.

Increasing anemia develops and takes the macrocytic type, with slight hyperchromia, lymphocytosis, and thrombopenia. The face is ashen. Abnormal pigmentation can be noted.

Evolution: Chronic or even intermittent.

Prognosis is rather serious. Marasmus finally causes the death of the patient.

DIAGNOSIS

Diagnosis is rather easy in typical cases. The trilogy of voluminous stools, glossitis, and emaciation is characteristic. X-rays show abnormalities in the mobility of the small intestine.

Sprue is distinguished from pernicious anemia of Addison-Biermer by emaciation, hypocalcemia and a normal bilirubinemia, moreover by the characteristic stools. Macrocyto-megaloblastosis, nervous lesions, lemon-colored complexion, total achylia (after histamine) belong to pernicious anemia. Pellagra shows stools with a normal amount of fats, a more moderate and generally microcytic anemia, exanthema, normal calcemia.

There is no special reason to distinguish sprue from sprue nostras or from the disease of Gee-Gerter, except, if need be, in the etiology.

TREATMENT

Rest in bed and a temperate climate are necessary. The diet will be poor in fats and carbohydrates, rich in proteins: raw meat, liver. Serious cases are benefited by fresh or pasteurized milk (without cream) and fruits (diet of strawberries, apples, and bananas).

Of considerable importance is the buccal or parenteral absorption of the main vitamins (Marmite, etc.). Administration of antipernicious hepatic extracts gives good results for the buccal troubles as well as those of the intestines. Parenteral administration is advisable.

Folic acid in ordinary dosis (20 mg. a day), thymin (5-methyl uracil, at the dosis of 15 Gm. a day) are recent discoveries.

Diarrhea, glossitis may demand symptomatic treatments (astringents, analgesics).

The weight of stools will be a valuable guide in the course of treatment. The latter should be carried to sufficient length with a careful and physiologic diet prescribed.

Prophylaxis: It is obscure. Alimentary hygiene, and the treatment of the chronic enterocolitis appear to be essential.

Burning Feet

This condition has been known for a long time as afflicting subjects suffering from malnutrition, pellagra, etc., and has been recently observed as of frequent occurrence in prisoners of war in Japanese hands. The name indicates the frequently intense pain suffered by the patients (the hands are seldom affected).

RECOMMENDED DIETARY ALLOWANCES[1] (Revised 1945)

Food and Nutrition Board, National Research Council, U.S.A.

The following dietary allowances have been recommended by the Food and Nutrition Board, National Research Council, U.S.A. To most nutritionists in warm countries these allowances appear as exceeding rather generously the normal requirements (ascorbic acid, for instance).

	Calories	Protein, Gm.	Calcium, Gm.	Iron, mg.	Vitamin A, I. U.[2]	Thiamin, mg.[3]	Riboflavin, mg.[3]	Niacin (Nicotinic acid), mg.[3]	Ascorbic acid, mg.	Vitamin D, I. U.
Man (154 lb., 70 Kg.)										
Sedentary	2,500	70	0.8	12[4]	5,000	1.2	1.6	12	75	[5]
Moderately active	3,000	70	0.8	12[4]	5,000	1.5	2.0	15	75	[5]
Very active	4,500	70	0.8	12[4]	5,000	2.0	2.6	20	75	[5]
Woman (123 lb., 56 Kg.)										
Sedentary	2,100	60	0.8	12	5,000	1.1	1.5	11	70	[5]
Moderately active	2,500	60	0.8	12	5,000	1.2	1.6	12	70	[5]
Very active	3,000	60	0.8	12	5,000	1.5	2.0	15	70	[5]
Pregnancy (latter half)	2,500[6]	85	1.5	15	6,000	1.8	2.5	18	100	400 to 800
Lactation	3,000	100	2.0	15	8,000	2.0	3.0	20	150	400 to 800
Children up to 12 yrs.[7]:										
Under 1 yr.[8]	100/2.2 lb. (1 Kg.)	3.5/2.2 lb. (1 Kg.)	1.0	6	1,500	0.4	0.6	4	30	400 to 800
1–3 yrs. (29 lb., 13 Kg.)	1,200	40	1.0	7	2,000	0.6	0.9	6	35	400
4–6 yrs. (42 lb., 19 Kg.)	1,600	50	1.0	8	2,500	0.8	1.2	8	50	400
7–9 yrs. (55 lb., 25 Kg.)	2,000	60	1.0	10	3,500	1.0	1.5	10	60	400
10–12 yrs. (75 lb., 34 Kg.)	2,500	70	1.2	12	4,500	1.2	1.8	12	75	400
Children over 12 yrs.[7]:										
Girls, 13–15 yrs. (108 lb., 49 Kg.)	2,600	80	1.3	15	5,000	1.3	2.0	13	80	400
16–20 yrs. (119 lb., 54 Kg.)	2,400	75	1.0	15	5,000	1.2	1.8	12	80	400
Boys, 13–15 yrs. (103 lb., 47 Kg.)	3,200	85	1.4	15	5,000	1.5	2.0	15	90	400
16–20 yrs. (141 lb., 64 Kg.)	3,800	100	1.4	15	6,000	1.8	2.5	18	100	400

[1] Tentative goal toward which to aim in planning practical dietaries; can be met by a good diet with a variety of natural foods. Such a diet will also provide other minerals and vitamins, the requirements for which are less well known.

[2] The allowance depends on the relative amounts of vitamin A and carotene. The allowances of the table are based on the premise that approximately two-thirds of the vitamin A value of the average diet in this country is contributed by carotene and that carotene has half or less than half the value of vitamin A.

[3] For adults (except pregnant and lactating women) receiving diets supplying 2,000 calories or less, such as reducing diets, the allowances of thiamine, riboflavin, and niacin may be 1 mg., 1.5 mg., and 10 mg., respectively. The fact that figures are given for different calorie levels for thiamine, riboflavin, and niacin does not imply that we can estimate the requirement of these factors within 500 calories, but they are added merely for simplicity of calculation. Other members of the B complex also are required, though no values can be given. Foods supplying adequate thiamine, riboflavin, and niacin will tend to supply sufficient of the remaining B vitamins.

[4] There is evidence that the male adult needs little or no iron. The allowance will be provided if the diet is satisfactory in other respects.

[5] For persons who have no opportunity for exposure to clear sunshine and for elderly persons, the ingestion of small amounts of vitamin D may be desirable. Other adults probably have little need for vitamin D.

[6] During the latter part of pregnancy the allowance should increase approximately 20 per cent over the preceding level. The value of 2,500 calories represents the allowance for pregnant sedentary women.

[7] Allowances for children are based on the needs for the middle year in each group (as 2, 5, 8, etc.) and are for moderate activity and for average weight at the middle year of the age group.

[8] Needs of infants increase from month to month with size and activity. The amounts given are for approximately 6 to 8 months. The dietary requirements for some of the nutrients such as protein and calcium are less if derived largely from human milk.

Simpson (1946) has described the coexistence of ocular troubles, amblyopia and even retrobulbar neuritis. Anesthesic troubles and lessening of the knee jerk have been observed. According to Simpson, the Kachang hijau (Kadjang idoe or Phaseolus radiata), at the dosis of 150 Gm. per day, cures the burning feet but not the eye troubles.

Thiamin alone has not been active. Other constituents of the vitamin B group must be considered. Harrison (1946) did not have much success with B vitamins. He rather advises the use of a vaso-dilatator: calcium gluconate, nicotinic acid, amyl nitrate. He believes that the mechanism may be a vascular spasm with rise of the diastolic pressure.

FURTHER RECOMMENDATIONS

(*See table, Recommended Dietary Allowances, page 393*)

Fat. There is available little information concerning the human requirement for fat. Fat allowances must be based at present more on food habits than on physiological requirements. While a requirement for certain unsaturated fatty acids (the linoleic and arachidonic acids of natural fats) has been amply demonstrated with experimental animals, the human need for these fatty acids is not known. In spite of the paucity of information on this subject there are several factors which make it desirable that fat be included in the diet to the extent of at least 20 to 25 per cent of the total calories and that the fat intake include "essential" unsaturated fatty acids to the extent of at least 1 per cent of the total calories. At higher levels of caloric expenditure, e.g., for a very active person consuming 4500 calories and for children and adolescent persons, it is desirable that 30 to 35 per cent of the total calories be derived from fat. Since foodstuffs such as meat, milk, cheese, and nuts may be expected to contribute "invisible" fat to the extent of from one-half to two-thirds of the total amounts of fat implied by the above proportions of the total calories, it is satisfactory to use separated or "visible" fats such as butter, margarine, lard, and shortenings only to the extent of one-third to one-half of the amounts indicated.

Copper. The requirement for copper for adults is about 1 to 2 mg. daily. Infants and children require approximately 0.05 mg. for each kilogram of body weight. The requirement for copper is approximately one-tenth that for iron. A good diet normally will supply sufficient copper.

Iodine. The requirement for iodine is small, probably about 0.002 to 0.004 mg. daily for each kilogram of body weight, or a total of 0.15 to 0.30 mg. daily for the adult. This need is met by the regular use of iodized salt; its use is especially important in *adolescence* and *pregnancy*.

Phosphorus. Available evidence indicates that the phosphorus allowances should be at least equal to those for calcium in the diets of children and of women during the latter part of pregnancy and during lactation. In the case of other adults the phosphorus allowances should be approximately 1.5 times those for calcium. In general it is safe to assume that if the calcium and protein needs are met through common foods, the phosphorus requirement also will be covered, because the common foods richest in calcium and protein are also the best sources of phosphorus.

Vitamin K. The requirement for vitamin K usually is satisfied by any good diet. Special consideration needs to be given to newborn infants. Physicians commonly give vitamin K either to the mother before delivery or to the infant immediately after birth.

Salt. The needs for salt and for water are closely interrelated. A liberal allowance of sodium chloride for the adult is 5 Gm. daily, except for some persons who sweat profusely. The average normal intake of salt is 10 to 15 Gm. daily, an amount which meets the salt requirements for a water intake up to 4 liters daily. When sweating is excessive, one additional gram of salt should be consumed for each liter of water in excess of 4 liters daily. With heavy work or in hot climates 20 to 30 Gm. daily may be consumed with meals and in drinking water. Even then, most persons do not need more salt than usually occurs in prepared foods. It has been shown that after acclimatization persons produce sweat that contains only about 0.5 Gm. to the liter in contrast with a content of 2 to 3 Gm. for sweat of the unacclimatized person. Consequently after acclimatization, need for increase of salt beyond that of ordinary food disappears.

Water. A suitable allowance of water for adults is 2.5 liters daily in most instances. An ordinary standard for diverse persons is one milliliter for each calorie of food. Most of this quantity is contained in prepared foods. At work or in hot weather, requirements may reach 5 to 13 liters daily. Water should be allowed *ad libitum,* since sensations of thirst usually serve as adequate guides to intake except for infants and sick persons.

Appendix A

SPECIALIZED CHEMICAL DRUGS

We have found it desirable to give a list of the synthetic chemical drugs specialized under different names which are used in the most important diseases of the warm climates.

The following abbreviations have been used:

C.N.	*Chemical name*
I.N.	*International name*
B.	*Belgium*
E.	*England*
F.	*France*
G.	*Germany*
S.	*Switzerland*
U.S.A.	*United States of America*
p.o.	*per os*
i.m.	*intramuscular*
i.v.	*intravenous*
s.c.	*subcutaneous*

GENERAL INFECTIONS

1. African Trypanosomiasis

Glyphenarsine (I.N.)

C.N.: Sodium N-phenyl glycinamide-p-arsonate
B.: Tryponarsyl
E.: Tryparsamide B.P.
F.: Tryparsamide
G.: Trypothan, Novatoxyl
U.S.A.: Tryparsamide
Doses: i.v. or i.m.: 2 to 3 Gm. repeated 10 to 20 times (weekly). Watch the vision.

Sodium Arsanilate (I.N.)

C.N.: Sodium p-aminophenyl-arsonate
B.: Irsanax
E.: Arsamin and Soamin
F.: Trypoxyl
G.: Atoxyl

Doses: p.o. 500 mg. (not much used). i.m. and i.v.: 500 mg. to 1 Gm. repeated 10 to 20 times (weekly). Watch the vision.

Suramin sodium (I.N.)
C.N.: Sodium salt of symmetric bis (m-aminobenzoyl-m-amino-p-methylbenzoyl-1-napthylamino-4-6-8-trisulfonic acid) carbamid
B.: Belganyl
E.: Antrypol, Suramin
F.: Moranyl, Foureau 309, Naganol
G.: Bayer 205, Germanin, Naganol
U.S.A.: Suramin, Naphuride sodium
Doses: i.v.: 1 to 2 Gm. Total cure 5 to 6 Gm. in 6 to 10 days. Can be repeated after one month.

Antimony (See Trystibine with schistosomiasis)

Diamidines (See below, 3. Leishmaniasis and Trypanosomiasis)

2. Leishmaniasis (Pentavalent Antimonials)

Neostibosan (I.N.)
C.N.: Diethylamine-p-amino-phenylstibinate
G.: Neostibosan, Bayer 693, von Heyden 693
Doses: i.v. and i.m. 200 mg. to 300 mg. Maximum doses 450 mg. 8 to 10 daily injections.

Solustibosan (I.N.)
C.N.: a pentavalent antimony compound of hexonic acid
E.: Stibatin, Pentostam
G.: Solustibosan
Doses: i.m. or i.v.: 6 cc. then 12 cc. of the solution of 2 per cent of SB per day for 10 days. Total dose: 120 cc. and more.

Stibamin Glucoside (I.N.)
C.N.: N-glucoside of sodium aminophenyl-p-stibinate of soda
E.: Neostam B.W.
Doses: i.v.: 200 mg.

Stibosan (I.N.)
C.N.: Sodium m-chlor-p-acetylaminophenylstibinate
G.: Stibosan or von Heyden 471 (no longer obtainable)
Doses: i.v. or i.m.: 200 mg. every two days. Total dose 6 to 10 Gm.

Stiburea (I.N.)
C.N.: a combination of urea and p-aminophenylstibinic acid
India: Urea stibamine
Doses: i.v. or i.m. 200 mg.

3. LEISHMANIASIS AND TRYPANOSOMIASIS (DIAMIDINE)

Diamidinostilbene B.P. (I.N.)

C.N.: 4-4′ diamidino stilbene hydroxyethane sulphonate (isethionate)

E.: Stilbamidine

Doses: i.v. 40 to 100 mg. per day for 10 to 15 consecutive days (make the solutions just before use and keep them in the dark). i.v. very slow with adrenalin. Total dose approximately 30 mg./Kg. body weight.

Diamidinophenoxypropane B.P. (I.N.)

C.N.: 4-4′ diamidino diphenoxypropane (isethionate)

E.: Propamidine and M & B 782

Doses: i.v. and i.m.: 30 mg. to 100 mg. for 10 consecutive days.

Diamidinophenoxypentane B.P. (I.N.)

C.N.: 4-4′ diamidinodiphenoxapentane under the form of hydroxyethanesulfonate

E.: Pentamidine and M & B 800

Doses: i.v. and i.m.: 30 to 150 mg.: 10 to 16 daily injections.

4. MALARIA

Atabrin (I.N.)

C.N.: 2 methoxy-6-chloro-9(α methyl-δ-diethylaminobutyl)-aminoacridine dihydrochloride

E.: Mepacrine or Quinacrine

F.: Quinacrine

G.: Atebrine

U.S.A.: Quinacrine hydrochloride or Mepacrine hydrochloride, Atabrin

Doses: p.o.: 300 mg. per day (600 to 900 mg. the first day, "loading dose"). Glucose and sodium bicarbonate. After the meals. Total dose 2 Gm. 800 mg. i.m. (methane sulfonate or chlorhydrate) 200 mg. 3 times per day and more. i.v. (not advisable). 100 mg.

Chloroquine S.N. 7618

C.N.: 7-chloro-4(4 diethylamino-1 methylbutylamino) quinoline diphosphate

U.S.A.: Aralen

Doses: p.o. 500 mg. 4 days.

Paludrine M. 4888 S.N. 12,837

C.N.:Chlorhydrate of N 1-p-chlorphenyl-N5-isopropylibiguanide

E.: Paludrine

Doses: p.o. 100 mg. 3 times per day for 10 consecutive days.

Pamaquin B.P. (*I.N.*)
C.N.: 8 diethyamino-isopentyl-amino 6 methoxyquinoline methylene bis oxynaphthoate
E.: Pamaquin, Plasmoquin, Praequine
F.: Praequine
G.: Plasmochin (chlorhydrate)
U.S.A.: Pamaquin naphtoate, Plasmoquin
Doses: p.o. 20 to 40 mg. per day for 3 to 5 days. After the meals. Sodium bicarbonate. Surveillance.

Pentaquine S.N. 13,276
C.N.: 6 methoxy-8(5-isopropylamino-amylamino)-quinoline
U.S.A.: Pentaquine
Doses: p.o. 10 mg. 4 times per day (with quinine). For 10 to 14 days.

Quiniostovarsol (*I.N.*)
C.N.: quinine salt of acetarsol
B.: Quinio-Goyl
F.: Quiniostovarsol, Malarsan
U.S.A.: Quinarsone
Doses: p.o. 250 mg. 2 to 4 times per day for 7 to 10 days. Surveillance.

Quinoplasmine: 10 mg. Plasmoquine plus 300 mg. Quinine sulfate
Doses: 1 tablet 3 times per day for 8 to 10 days, after the meals.
Remark: Recommended after a treatment with atabrin.

5. Bacterial Infections (Sulfonamides)

Irgafene (Switzerland)
C.N.: N 1-3-4 dimethylbenzoylsulfonilamide
Doses: p.o. per day: 5 Gm.-4 Gm.-3 Gm., then 2 to 3 Gm. and 1 to 2 Gm. (severe cases) or 3 to 4 Gm.-3 Gm.-2 Gm.-1 Gm., total 10 to 11 Gm. (average cases). Also used in injections.

Sulphacetamide (*I.N.*)
C.N.: p-aminobenzene sulfonacetamide
G.: Albucid
U.S.A.: Sulfacetamide
Doses: p.o. 6 to 8 Gm. per day for 5 to 7 days.

Sulfadiazine (*I.N.*)
C.N.: 2-p-aminobenzene sulfonamido pyrimidine
B.: Ucediazine
E.: Sulphadiazine
F.: Adiazine and Sopradiazine
G.: Pyrimal

U.S.A.: Sulfadiazine
Doses: p.o. 6 to 12 Gm. per day for 5 to 7 days. Alkalinize the urine.

Sulfanilamide or *Sulphanilamide (I.N.)*
C.N.: p-aminobenzene sulfonamide
B.: Astreptine
E.: Sulphanilamide
F.: Rubiazol A, Sulfamidyl, Streptocide, Lysococcine
G.: Prontosil Album
U.S.A.: Sulfanilamide
Doses: p.o. or in injections: 6 to 8 Gm. per day for 5 to 7 days.

Sulfapyridine (I.N.)
C.N.: 2-p-aminobenzene sulfonamide pyridine
B.: Sulfapyridine
E.: Dagenan
F.: Dagenan
G.: Eubasin
U.S.A.: Sulfapyridine
Doses: p.o. 5 to 7 Gm. per day. Also i.m. and i.v. Much liquid intake.

Sulfathiazol (I.N.)
C.N.: 2-p-aminobenzene sulfonamidothiazol
B.: Thiacoccine
E.: Thiazomide
F.: Thiazomide
G.: Eleudrom
S.: Cibazol
U.S.A.: Sulfathiazol
Doses: p.o. 6 to 10 Gm. per day for 5 to 7 days. Also i.m. and i.v. Alkalize the urine.

INTESTINAL DISEASES

1. BACILLARY DYSENTERY

Remark: The common sulfonamides with strong resorption can also be used.

Sulfaguanidine (I.N.)
C.N.: p-aminobenzesulfonylguanidine
E.: Sulphaguanidine
F.: Ganidan
S.: Sulfaguanidine, Sulfaguanyl
U.S.A.: Sulfaguanidine
Doses: p.o. 5 to 20 Gm. per day.

Succinylsulfathiazol (*I.N.*)

C.N.: 2-p-succinyl aminobenzene sulfonamidothiazol
B.: Sulfenterone
E.: Succinylsulphathiazol
U.S.A.: Sulfasuxidine, Colistatin
Doses: 10 to 14 Gm. per day p.o.

2. Amebiasis

Acetphenarsine (*I.N.*) Pentavalent As

C.N.: 3 acetylamino-4-hydroxyphenylarsonic acid
B.: Goyl
E.: Acetarsol
F.: Stovarsol
G.: Spirocid
S.: Trepocid
U.S.A.: Acetarsol, Acetarsone
Doses: p.o. 250 mg. 2 to 3 times per day for 4 days. Surveillance.

Carbarsone (*I.N.*) Pentavalent As

C.N.: 4 carbaminophenylarsonic acid
E.: Carbarsone
G.: Arsuran
U.S.A.: Carbarsone
Doses: p.o. 250 mg. 2 times per day for 8 to 10 days. Surveillance.

Chiniofon B.P. (*I.N.*)

C.N.: Sodium 7 iodo-8-hydroxy quinoline-5-sulfonate
B.: Chardyl
E.: Quinoxyl-Chiniofon
F.: Mixiod
G.: Yatren
U.S.A.: Chiniofon
Doses: p.o. from 750 mg. to 2.25 Gm., i.e., 250 to 750 mg. three times per day after the meals. Treatment lasts a week. Also in enema (1 to 1.5 per cent up to 3 Gm. of the product). Should not be boiled.

Diodoquin (*I.N.*)

C.N.: 5-7-diiodo-8-hydroxyquinoline
B.: Paramibe
U.S.A.: Diodoquin
Doses: p.o. 250 mg. 3 to 6 times per day for 10 days.

Iodochlorhydroxyquinoline (I.N.)
C.N.: 7-iodo-5-chlor-8-hydroxyquinoline
S.: Enterovioforme
Doses: 250 mg. 3 to 4 times per day for 5 to 10 days.

Rivanol (I.N.)
C.N.: 2 ethoxy-6-9-diaminoacridine lactate
G.: Rivanol
U.S.A.: Rivanol
Doses: 25 to 50 mg. 3 times per day. Preferably enemas (1/5000).

3. VERMIFUGES

Remark: Vermifuges are always prescribed after fasting and followed by purgative.

Ascaridol
G.: Ascaridol
Doses: 300 mg. 3 times per day at $^1/_2$-hour interval. Strong purgative one hour after the last intake.
Remark: For children, prescribe solution in castor oil.

Chenopod Oil
Doses: 0.75 cc. twice at one-hour interval. Sodium sulphate one hour later.
Remark: For children, prepare a solution of Chenopod oil in castor oil.

Diphenan B.P. (I.N.)
C.N.: p-benzylphenylcarbamate
E.: Diphenan
G.: Butolan
Doses: p.o. 3 times per day 500 mg. for one week.

Hexylresorcinol (I.N.)
C.N.: 1-3-dihydroxy-4-hexylbenzene
F.: Hexorcene, Felicol
U.S.A.: Caprokol
Doses: p.o. 200 mg. 5 times per day.

Phenothiazine (I.N.)
C.N.: Thiodiphenylamine
B.: Nematocid
E.: Phenothiazine
F.: Phenothian
U.S.A.: Phenothiazine
Doses: 4 to 8 Gm. in 4 days.

4. SCHISTOSOMIASIS

Anthiomaline (I.N.)

C.N.: Lithium antimonythiomalate
E.: Anthiomaline
F.: Anthiomaline
Doses: i.v. and i.m.: 30 to 120 mg. every second day. 10 injections.

Stibilase (I.N.)

C.N.: Diethylamine antimonyl dehydroxyquinoline sulphonate
B.: Stibilase
Doses: i.v.: 250 mg. 10 times every second day.

Stibophen B.P. (I.N.)

C.N.: Sodium antimony III bispyrocatechol-3-5-sodium disulfonate
E.: Stibophen
G.: Fouadin and Neoantimosan
Doses: i.v. and i.m. 100 to 300 mg. in 7 per cent solution. Total cure 40 cc.

Trystibine (I.N.)

C.N.: Sodium antimonyl-7-amino-8-hydroxyquinoline sulphonate N methylene sulphite
B.: Trystibine
Doses: i.v. 250 to 500 mg. 1 or 2 times a week.

SKIN DISEASES

SYPHILIS, YAWS, SPIROCHETOSES

Dichlorophenarsine hydrochloride (I.N.) Trivalent As

C.N.: 3 amino 4 hydroxyphenyldichlorarsine hydrochloride
B.: Dipharsine
F.: Fontarsol
U.S.A.: Dichlorophenarsine and Dichlor-mapharsen, Chlorarsen
Doses: i.v. 60 to 100 mg. twice a week. Total dose: 1.5 to 3 Gm.

Ethylacetphenarsine (I.N.) Pentavalent As

C.N.: Diethylamine salt of acetarsol
B.: Golarsyl
E.: Acetylarsan
F.: Acetylarsan
Doses: i.m. or s.c. 1 to 3 cc. of the 23.6 per cent solution (50 mg. As/cc.) once or twice a week. 8 to 10 weeks.

Neoarsphenamine (*I.N.*) Trivalent As

C.N.: Sodium 3-3′ diamino-4-4′ dihydroxyarsenobenzene N-methylene sulfoxylate

B.: Arsebenyl

E.: Novarsenobillon, Neoarsphenamine, Neokharsivan

F.: Novarsenobenzol, Rhodarsan

G.: Neosalvarsan

S.: Neomesarca

U.S.A.: Neoarsphenamine

Doses: i.v. 150 to 900 mg. Total dosage: 4 to 6 Gm. for one series. 2 to 7 days space between the injections according to the doses.

Oxophenarsine hydrochloride (*I.N.*)

C.N.: 3-amino-4-hydroxyphenylarsenoxyde hydrochloride

E.: Neohalarsine (very close, tartrate, 60 to 90 mg. once or twice a week)

F.: Fontarsan

U.S.A.: Mapharside, Mapharsen

Doses: i.v. 40 to 60 mg. (90 with the tartrate). Two injections i.v. a week.

Sodium Acetphenarsine (*I.N.*) Pentavalent As

C.N.: Sodium 3-acetylamino-4-hydroxyphenylarsonate

B.: Goyl sodique

E.: Acetarsol Sodium

F.: Stovarsol sodique

Doses: i.m. or s.c.: 500 mg. to 1 Gm. 20 injections every second day. Surveillance. (Vision and kidneys.)

Sulpharsphenamine B.P. (*I.N.*) Trivalent As

C.N.: Sodium 3-3′ diamino-4-4′ dihydroxy arsenobenzene-N-N′ dimethylene sulfite

B.: Sulfarsebenyl

E.: Sulpharsphenamine-Metarsenobillon

F.: Sulfarsenol

G.: Myosalvarsan

S.: Sulfomesarca

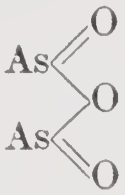
U.S.A.: Sulpharsphenamine

Doses: i.m. or s.c.: 100 to 600 mg. as with Neoarsphenamine.

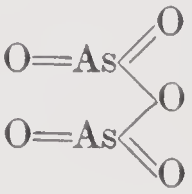
Appendix B

FORMULAS OF SOME CHEMICAL DRUGS

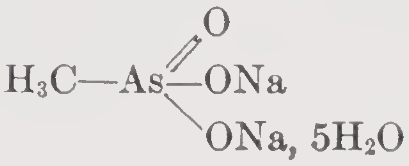
Arsenious Acid



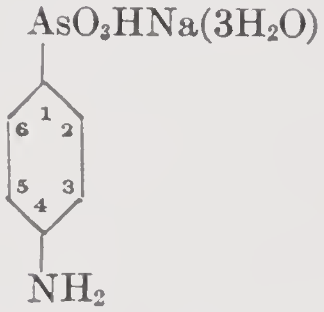
Arsenic Acid



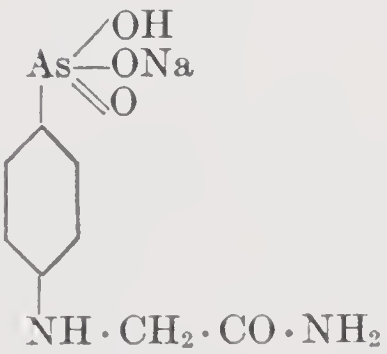
Sodium Methylarsonate



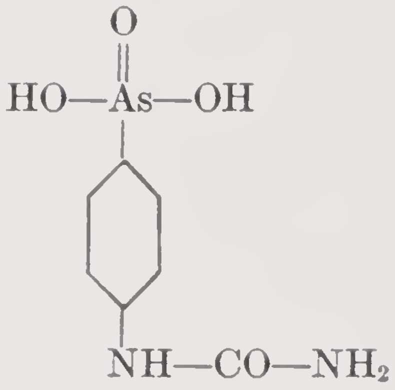
Atoxyl



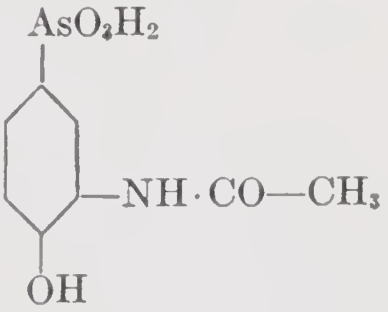
Tryparsamide



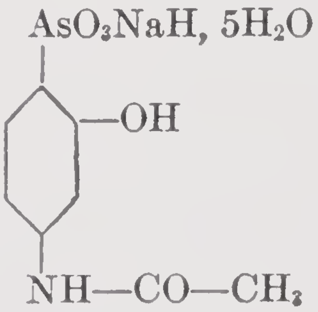
Carbarsone



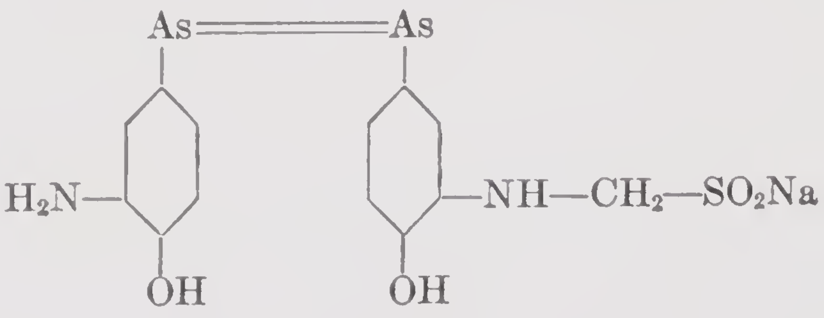
Stovarsol



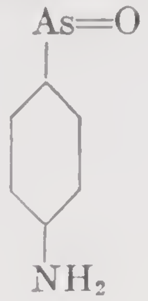
Sodium Orsanine



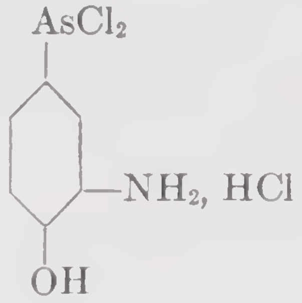
Neoarsphenamine (Neosalvarsan)



p-Aminophenyl Arsinoxide

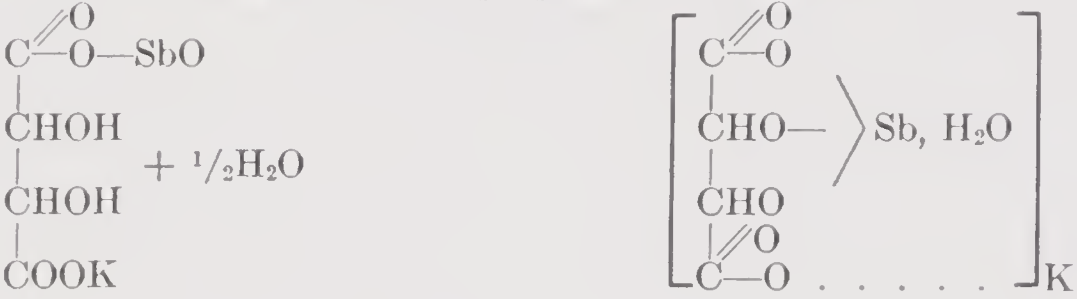


Halarsol

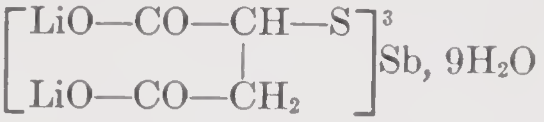


Antimony Potassium Tartrate (Tartar Emetic)

Two of several proposed formulae

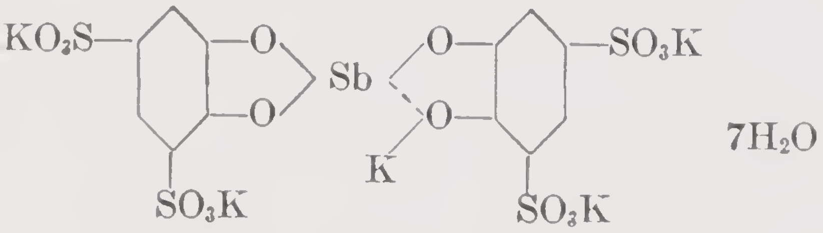


Antimony Lithium Thiomalate (Anthiomaline)



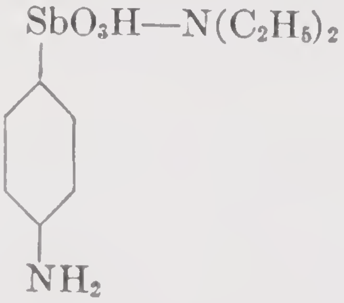
$$\left[\begin{array}{l} \text{LiO—CO—CH—S} \\ \qquad\qquad\quad | \\ \text{LiO—CO—CH}_2 \end{array}\right]^3 \text{Sb}, 9H_2O$$

Antimosan and Fuadin (Na replaces K in the latter)

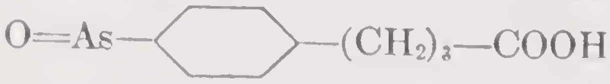


Phenylstibinic Acid

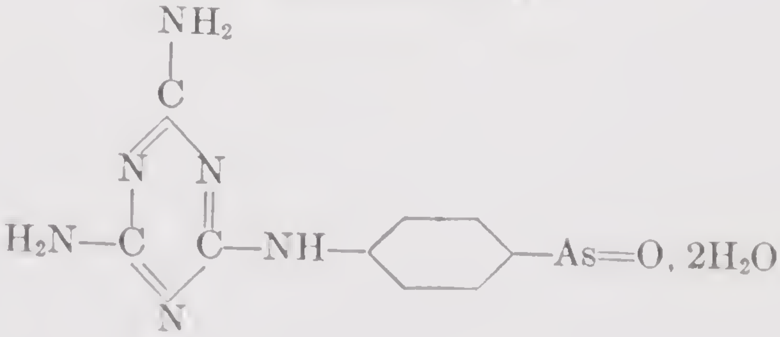
Diethylamine p-amino phenylstibinate (neostibosan)



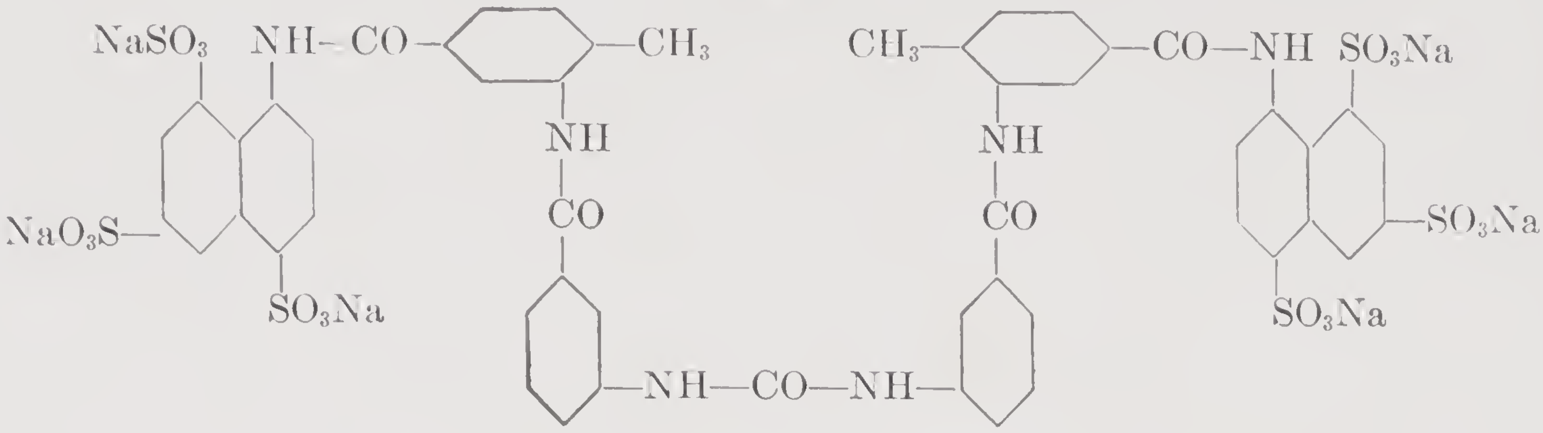
γ(p-Arsenosophenyl) Butyric Acid



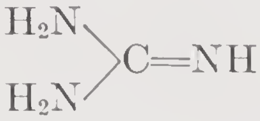
Melarsen Oxide



Germanin

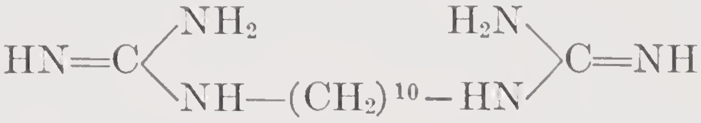


Guanidine



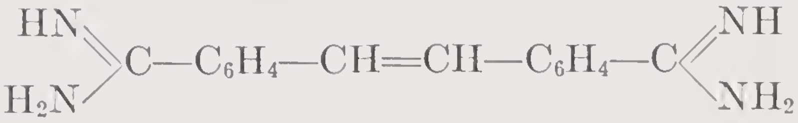
$$\begin{matrix} H_2N \diagdown & \\ & C{=}NH \\ H_2N \diagup & \end{matrix}$$

Synthaline (Decamethylen diguanidine)



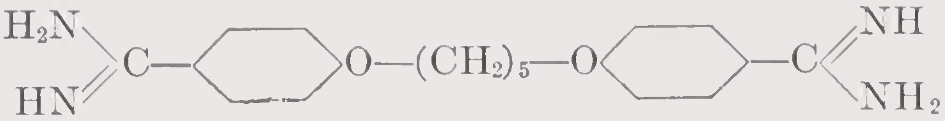
$$HN{=}C\begin{matrix} \diagup NH_2 \\ \diagdown NH \end{matrix}\!-\!(CH_2)^{10}-\begin{matrix} H_2N \diagdown \\ HN \diagup \end{matrix}C{=}NH$$

Diamidinostilbene (Stilbamidin)

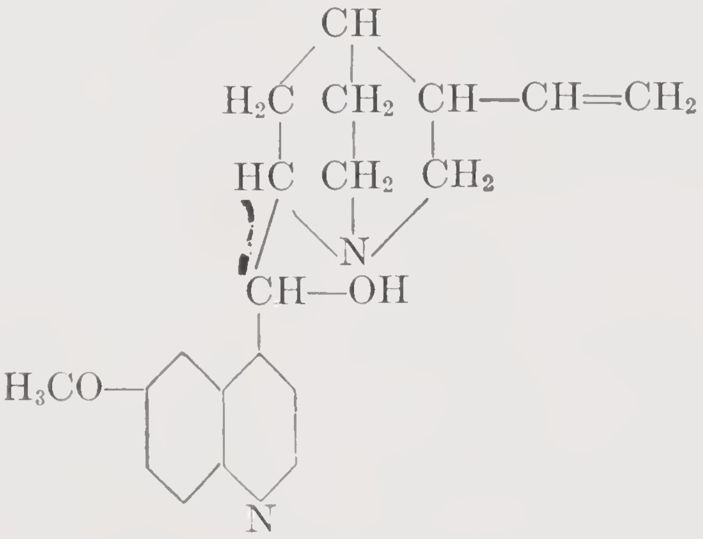


$$\begin{matrix} HN \diagdown \\ H_2N \diagup \end{matrix}C—C_6H_4—CH{=}CH—C_6H_4—C\begin{matrix} \diagup NH \\ \diagdown NH_2 \end{matrix}$$

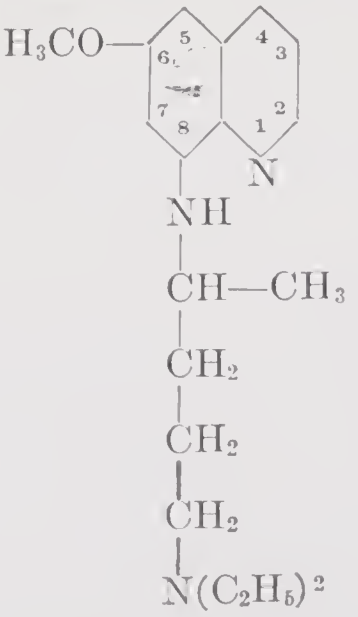
Pentamidine



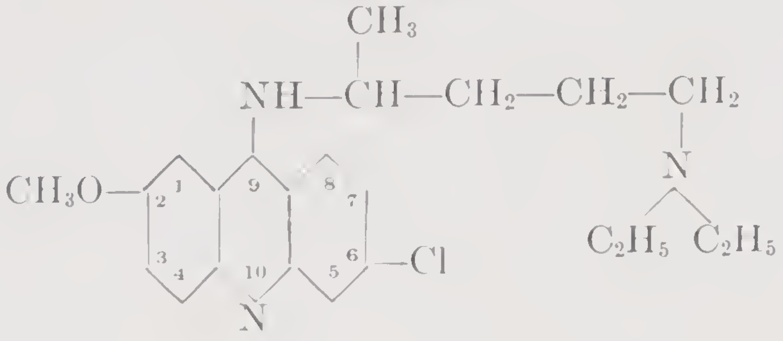
Quinine (and Quinidine)



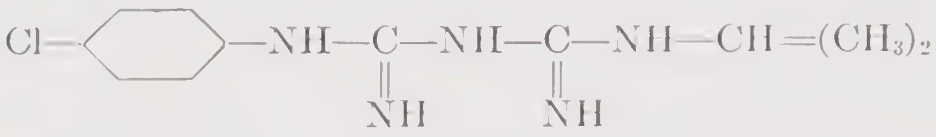
Plasmochin, Pamaquin



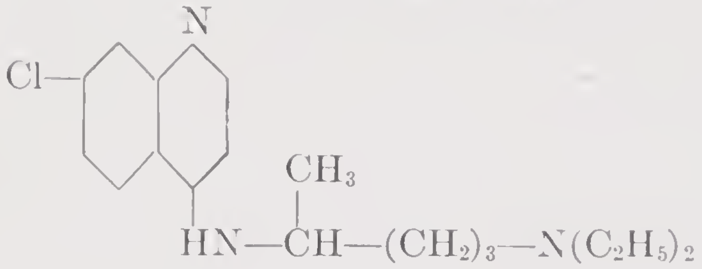
Atabrin



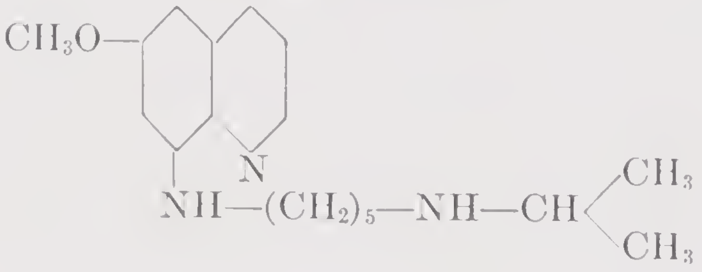
Paludrine



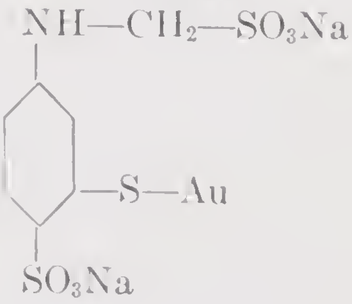
Chloroquine (SN 7618)



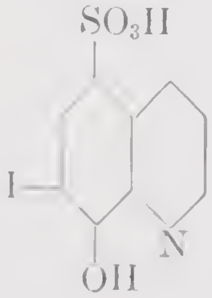
Pentaquine (SN 13276)



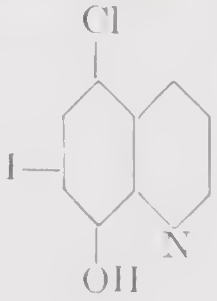
Solganal



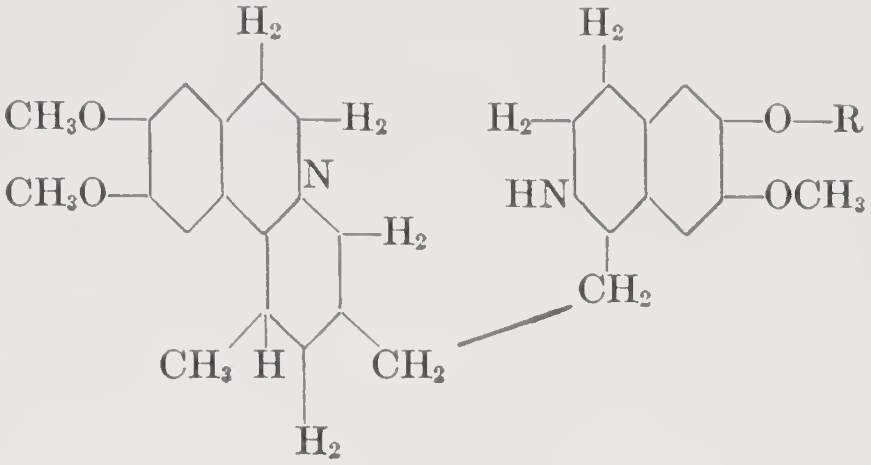
Yatren



Vioform

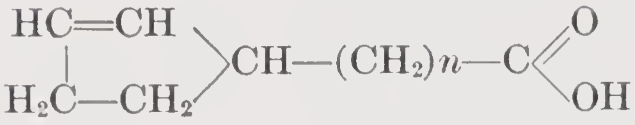


Emetine

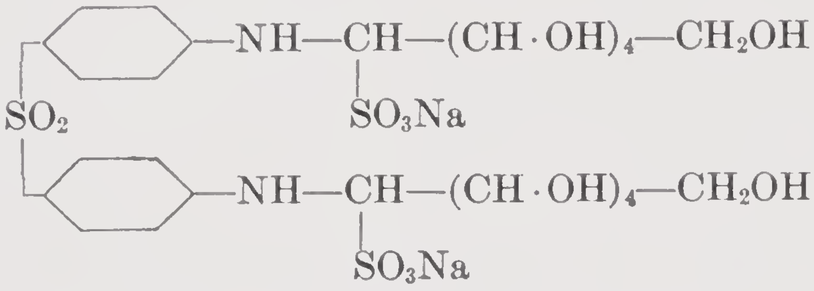


Emetine (R = CH_3)
Cephacline (R = H)

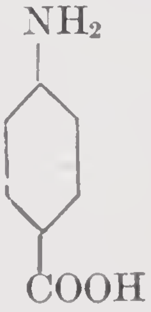
Hydnocarpic acid: $n = 10$
Chaulmoogric acid: $n = 12$



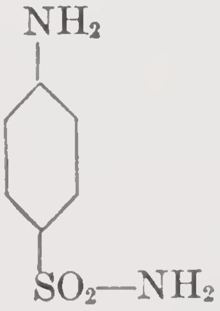
Promin



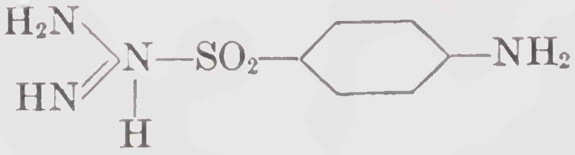
p-Amino-benzoic acid



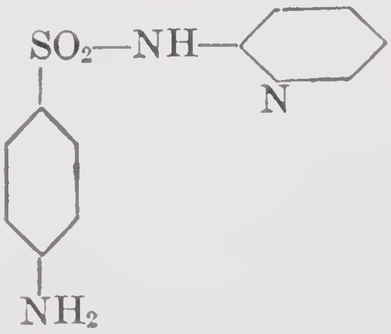
Sulphanilamide



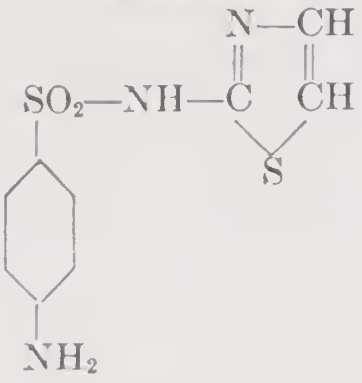
Sulphaguanidine



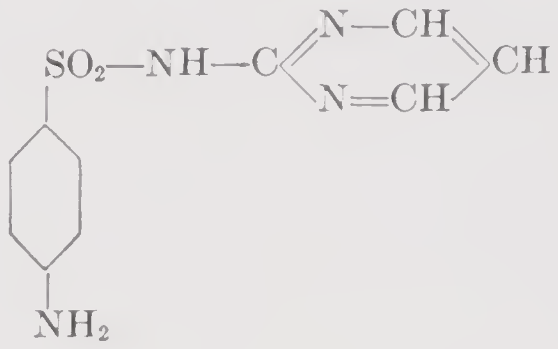
Sulphapyridine



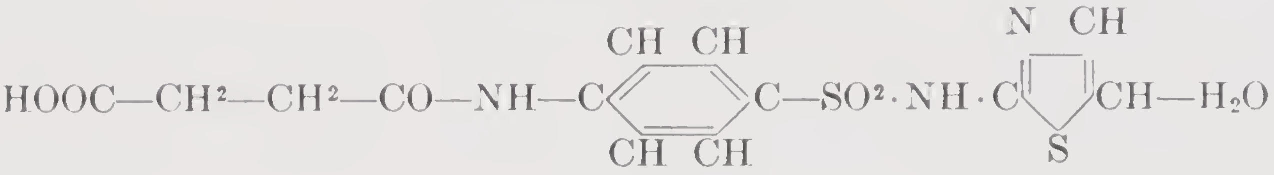
Sulphathiazole



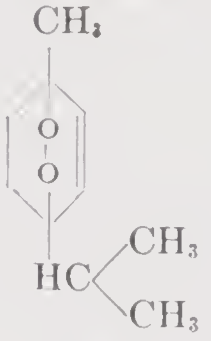
Sulphapyrimidine



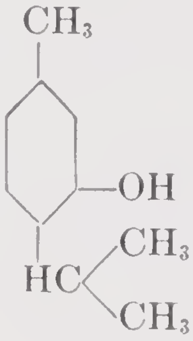
Succinyl sulphathiazol



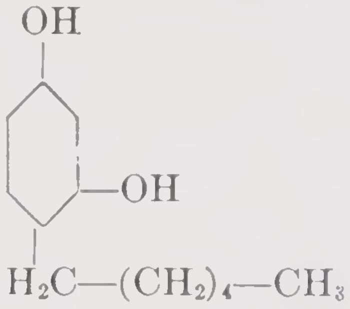
Ascaridol



Thymol



Hexylresorcinol



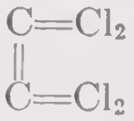
Chloroform

$H—C\equiv Cl_3$

Carbon Tetrachloride

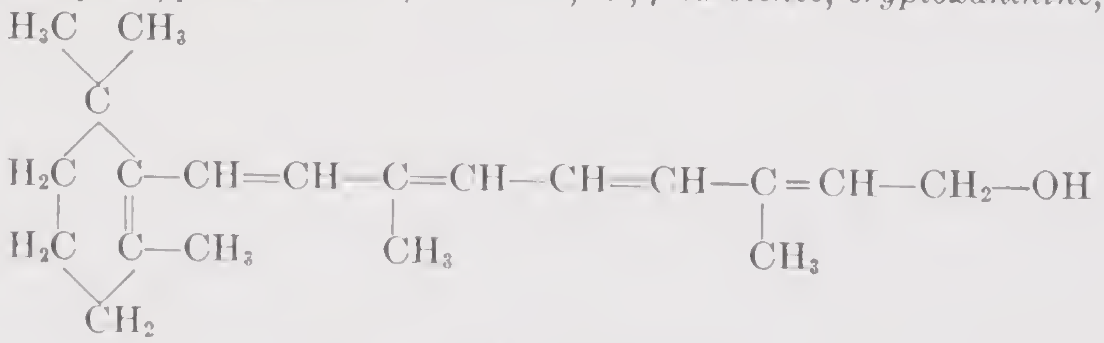
CCl_4

Tetrachlorethylene



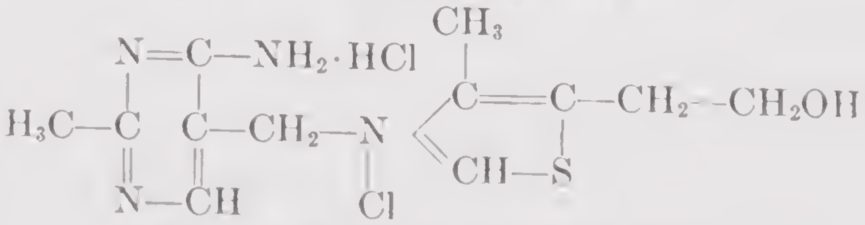
$$\begin{array}{l} C=Cl_2 \\ \| \\ C=Cl_2 \end{array}$$

Vitamin A (*axerophtol, provitamins: β-carotene, α-,γ-carotenes, cryptoxanthine, aphanine*)



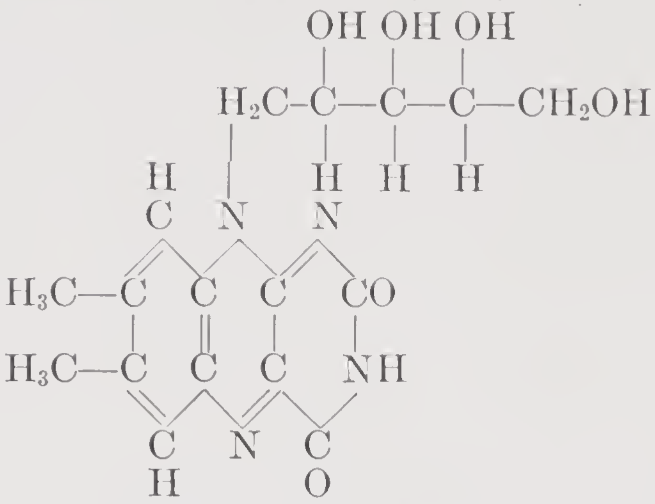
Vitamin A: $C_{20}H_{29}OH$

Vitamin B₁, Aneurine, thiamine



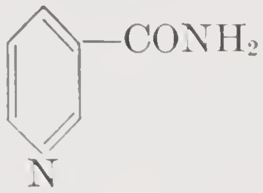
Vitamin B₁: $C_{12}H_{17}ON_4SCl\cdot HCl$

Vitamin B_2, Lactoflavine, riboflavine



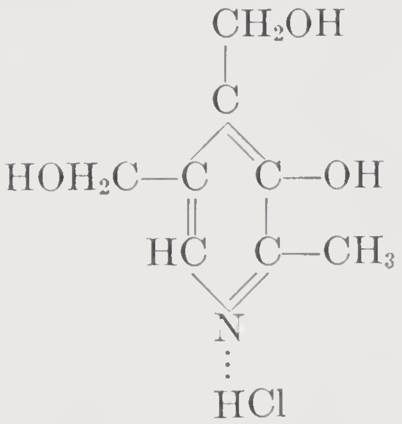
Vitamin B_2: $C_{17}H_{20}O_6N_4$

Nicotylamide, Factor PP



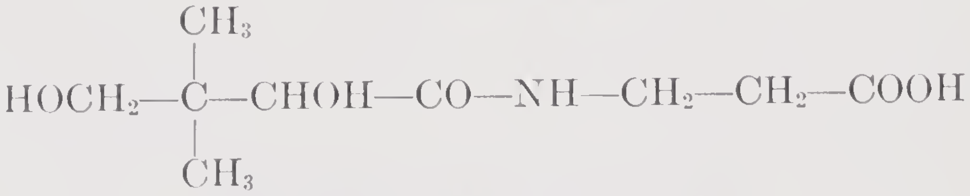
Nicotinic acid amide: $C_6H_6ON_2$

Vitamin B_6, Adermine, pyridoxine



Pyridoxine hydrochloride
Vitamin B_6: $C_8H_{11}O_3N \cdot HCl$

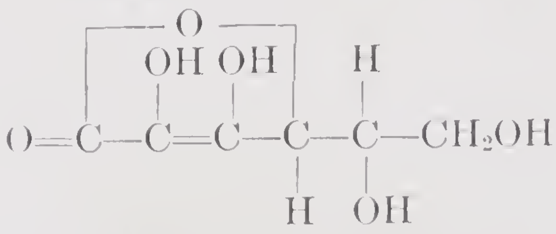
Pantothenic Acid



$$HOCH_2{-}\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}{-}CHOH{-}CO{-}NH{-}CH_2{-}CH_2{-}COOH$$

Pantothenic acid, $C_9H_{17}O_5N$

Vitamin C, l-Ascorbic Acid



Vitamin C: $C_6H_8O_6$

Appendix C

SIMPLE LABORATORY PROCEDURES LEADING TO THE DIAGNOSIS OF THE DISEASES OF WARM CLIMATES

The most important diseases of the warm climates can be diagnosed with certainty only after the discovery of the specific parasite (larva, adult or its eggs) or of certain cellular changes in the blood, the cerebrospinal fluid, the feces, the urine, or the skin of the patients.

The practitioner in tropical regions being often isolated from a laboratory is therefore lost unless he himself uses a microscope and practices a few simple laboratory technics. Even outside the tropics, all medical men should be fully aware of the fact that the etiology of certain fevers cannot be discovered by consultation and the use of classic bacteriologic methods. Any patient who has lived or merely passed through a warm climate, be it tropical, subtropical, or even temperate, should be suspected of having acquired a tropical disease until adequate examination has been performed by a competent laboratory.

The simpler microscopic procedures that any practitioner should eventually have to perform himself are therefore given in this appendix, namely, the essential bacteriologic stainings (general diseases and skin diseases), the morphologic study of the blood and bone marrow, and the staining of the blood parasites (general diseases), the microscopic stool and urine examination (intestinal diseases), the research of fungi (mainly skin diseases).

The culture mediums and the biochemical analyses are not given here because only a well equipped and specialized laboratory can execute them accurately. Excellent manuals on laboratory methods and microscopic methods will provide ample information.

Three preliminary remarks must be stressed concerning the microscopic technic:

1. The microscope should provide three magnifications in the range of 50 to 100 (objective × 10), 200 to 400 (objective × 40), and 600 to 1000 (objective × 90 or 100). The latter necessitates an immersion lens. Cedar oil is the classic immersion medium. Substitutes have been used recently. An excellent thin immersion oil is made of heavy mineral oil (U.S.P.) 82 parts with alpha-bromnaphthalene 18 parts. A small amount of it left on the stained blood film acts as a preservative. The fading of the staining by xylol (used to dissolve cedar oil) is also avoided in the latter method.

When none of these immersion mediums is available, paraffin oil or castor oil may be used, but with less favorable results.

2. The microscopic preparations must be made on clean slides, preferably new ones, well washed and grease-free. The use of new slides is imperative for the diagnosis of acid-fast bacilli (leprosy).

The wet preparations must be sterilized in water containing an antiseptic (2 to 5 per cent cresol solution). Stained preparations, whether covered or not with oil or Canada balsam, must be soaked first in a mixture of xylol and alcohol 95° in almost equal proportions. Alcohol should be added until the mixture is clear. The preparations are then rinsed thoroughly in running water.

Before re-using the glass slides, more elaborate cleaning methods are required:

(a) Boil in soapy water.

(b) Rinse in tap water.

(c) Soak for 48 hours in: potassium dichromate, 50 Gm.; sulfuric acid, 100 Gm.; water, 1,000 Gm.

(d) Rinse in tap water.

(e) Wash in alcohol 70 per cent.

(f) Dry and polish. Store the slides wrapped in paper.

3. Ordinary glass slides are easily altered by a warm and humid climate. Slides made of green glass are more resistant, especially when kept in a 5 per cent chlorhydric acid water solution and in darkness. Special resistant glass slides are also available.

* * *

I. BACTERIOLOGIC STAININGS

Films are prepared with fresh material. Thick pus or mucus should be spread on the slide with a platinum loop. Dry in air. Fix by heating over flame or by applying alcohol.

1. *Simple Staining Methods:* All common bacteria are stained with the hydro-alcoholic solutions of the so-called basic dyes. The acid-fast bacteria show a lighter color. The spores remain unstained.

The following stains are commonly used for routine work:

Kolle's Blue	Carbol Thionine	Kuhne's Blue
Methylene Blue, 2 Gm. Sodium borate 5 per cent, 100 cc. Keeps very well	Thionine, 500 mg. Alcohol 95°, 10 cc. Phenol cryst., 8 Gm. Mix and leave for 24 hours in flask. Then add water to a volume of 100 cc. A few days' aging is necessary. Keeps several weeks.	Methylene blue, 1 Gm. Phenol cryst., 2 Gm. Dist. water, 100 cc. Keeps very well.

Carbolfuchsin (see further, the Ziehl-Neelsen method), diluted $^1/_5$ or $^1/_{10}$, also stains well.

All these dyes provide a good staining of the common bacteria after 30 to 60 seconds.

Wash, blot dry, and examine with immersion objective.

2. *Gram's Method:*

Reagents: (a) Crystal violet, saturated alcoholic solution 20 cc., ammonium oxalate 1 per cent aqueous, 80 cc. (Keeps a few weeks.)

(b) Iodine 1 Gm., potassium iodide 2 Gm., distilled water 300 cc.

(c) 95 per cent alcohol or acetone.

(d) Aqueous solution of safranine or Bismark brown or carbolfuchsine diluted $^1/_{10}$.

Technic: Air dry smears fixed over flame. Apply (a) for one to two minutes. Pour off. Add (b) for one minute. Wash in water. Decolorize with (c) until no traces of (a) are found. Wash and counterstain with (d) for one minute. Wash, blot, and dry in air.

Interpretation: Gram-positive organisms retain the violet color, Gram-negative lose it and take the counterstain. Newly prepared stains should be probed with known Gram-positive and Gram-negative organisms.

3. *Ziehl-Neelsen's Method:*

Reagents: (a) Saturated alcoholic solution of basic fuchsin 10 cc. and 5 per cent solution of phenol 90 cc.

(b) 3 cc. of hydrochloric acid with 95° ethyl alcohol to a volume of 100 cc.

(c) Saturated alcoholic solution of methylene blue 30 cc. with 0.01 per cent solution of KOH (0.1 cc. of 10 per cent KOH in 100 cc. distilled water) 70 cc.

Technic: Air dry smears fixed over flame. Apply (a) and heat gently for five minutes until steam appears over surface. Wash in water. Decolorize with (b). Wash in water and counterstain with (c) for one minute. Wash, blot, and dry in air.

Interpretation: Acid-fast organisms (genus Mycobacterium) are stained red while non-acid-fast organisms are stained blue.

4. *Fontana-Tribondeau's Method:*

Reagents: (a) Glacial acetic acid 1 cc., formalin (40 per cent) 2 cc.; distilled water 100 cc. (Ruge's solution).

(b) Phenol (liq. crystals) 1 cc., tannic acid 5 Gm., distilled water 100 cc.

(c) Silver nitrate 0.25 Gm., distilled water 100 cc. (brown glass). Before use, add to a part of the solution, drop by drop, a dilute solution of ammonia until the first produced precipitate is dissolved. Then carefully add a few drops of the silver nitrate solution until a faint opalescence is obtained. (Keeps several months.)

Technic: Thin air dry smears are fixed with (a) for one or two minutes and the solution is renewed. Wash in distilled water. Apply the mordant (b) and heat gently until steam appears for one minute. Wash in distilled water. Rinse with (c) and apply fresh solution, heating until steam rises. Wash, blot, and dry in air.

Interpretation: Spirochetes appear black on a light brown background (syphilis and yaws).

The spirochetes in the tissues are also shown by the *Giemsa* staining (see further the staining methods of the blood parasites) heated and renewed three times. The blood spirochetes (relapsing fever) are best colored with the *Giemsa* stain.

5. *Machiavello Stain:* (for Rickettsiae):

Reagents: (a) Saturated alcoholic solution of basic fuchsine.

(b) Aqueous solution of thionine 2 per cent.

(c) Buffer solution (pH 7.4–7.6) mixing 12 cc. of 1 per cent monobasic potassium phosphate with 88 cc. of 2.5 per cent of dibasic sodium phosphate.

(d) Aqueous solution of citric acid 0.5 per cent.

Mixture A is made of 1 cc. of (a) with 250 cc. of (c), filtered through filter paper and dropped onto the slide (does not keep).

Mixture B is made of double distilled water, 75 cc.; solution (d), 25 cc.; solution (b) 0.5 cc., and filtered (keeps well).

Technic: The smear is dried in air and stained by mixture A for three minutes, then washed with tap water. Pour mixture B on and off quickly (2 to 3 seconds) and rinse off with tap water.

II. Morphologic Study of the Blood and Bone Marrow

STAINING OF BLOOD PARASITES

Three different preparations are used:

(a) *Wet preparation:* A minute drop of peripheral or venous blood is examined, spread between slide and cover slip. The edges of the preparation are eventually sealed with vaseline. This method is particularly useful for mobile parasites (trypanosomes, microfilariae). Dark-field illumination allows the discovery of spirochetes. Centrifuged blood (triple centrifugation) and lymph node fluid are also examined in wet preparations (see section on African Trypanosomiasis).

(b) *Thin smears:* A small drop of blood is placed at 1 cm. from the end of a clean slide and evenly spread with the end of another slide which has been one-third narrowed by breaking a corner. While spreading the blood, the two slides should be held at an angle of 30°. The smear is then dried at once by waving it in the air. Immediate fixing is necessary as unfixed smears may be eaten by insects. Smears should also be stained as soon as possible, within two weeks at the most, as their staining characteristics change. Clean glassware, a thin film rapid drying and a not too delayed fixing and staining provide the best preparations. The thin smears are usually stained with the *May-Grünwald, Giemsa,* or the *Wright* stains (see further).

(c) *Thick smear:* A larger drop of blood is placed in the middle of the slide and spread with a pin, match, or glass rod, eliminating at the same time the fibrin, over a square surface approximately the size of a cover slip (4 sq. cm.). The size of the drop must be such that when the slide is held vertically after the spreading, no running of the blood occurs. The slide is then kept flat and the smear allowed to dry.

The thick smear preparation should not be fixed, but treated by stain diluted in distilled water. The erythrocytes are hemolyzed and therefore not seen on the final preparation, leaving a clear field on which only the leukocytes and the exo- or endoerythrocytic parasites are shown.

Although the morphologic details are not so clear as on the thin smear preparations, the diagnosis is always easy. The great advantage of the method lies in the fact that more parasites are found on a smaller area, saving a considerable amount of time and fatigue. For the past 25 years the Belgian school of tropical medicine has always considered that the thick smear was the most practical and, therefore, fundamental method for the diagnosis of malaria, relapsing fever, filariasis, and trypanosomiasis.

* * *

The customary staining method for the study of the blood and the blood parasites uses oxidized eosinate of methylene blue, as advocated by Romanowsky, and derived from the action of eosin on methylene blue followed by aging of the solution ("azur"). Many stains are based on the Romanowsky method. Those most used are the *Giemsa* (preceded or not by the *May-Grünwald* stain which is plain eosinate of methylene blue) and the *Wright.*

All the Romanowsky stains need to be diluted with a slightly acid (pH 6.4 to 6.6) or neutral (pH 7.0 to 7.2) distilled water. Phenol red (0.02 per cent solution) is used as an indicator.

The neutral buffers seem more satisfactory for a selective staining of the blood protozoa.

The following buffers should be tested with the available Romanowsky stains and chosen according to the results:

Potassium Phosphate (monobasic), 9.078 Gm. per liter	Sodium Phosphate (dibasic) 2 aq., 11.876 Gm. per liter		pH
90 cc.	10 cc.		7.65
80 cc.	20 cc.		7.35
70 cc.	30 cc.	Dilute each to 1000 cc.	7.15
60 cc.	40 cc.		6.98
50 cc.	50 cc.		6.81
40 cc.	60 cc.		6.64
30 cc.	70 cc.		6.47
20 cc.	80 cc.		6.24
10 cc.	90 cc.		5.91

If the proper reaction has been reached, the erythrocytes are reddish polychrome, the granules of the neutrophils lilac, of the basophils blue, and of the eosinophils orange red, the cytoplasm of the lymphocytes and the young bone marrow cells blue, the nuclei of the leukocytes purple red and the nuclei of the protozoa bright red. If the solution is too acid, the nuclei of the leukocytes are pale or colorless. If it is too basic all the cells are blue including the erythrocytes.

The preparations should be placed face downward in the staining solutions. This avoids the deposits of precipitates on the smears. The use of containers with curved bottoms (such as large watch glasses, or, better still, glass or plastic segments of cylinders about 20 cm. long and 10 cm. wide, in order to hold half a dozen slides) is therefore most convenient.

1. *Giemsa Stain.* The stock solution is made of:

Azur II eosin	3.0 Gm.
Azur II	0.8 Gm.
Glycerin	250. cc.
Methyl alcohol (chemically pure)	250. cc.

The stain improves with age through oxidation.

Technic: (a) Fix the thin smear with alcohol first. A thick smear preparation, on the contrary, should not be fixed previously.

(b) Stain fifteen to thirty minutes, the time being determined by trial, with a solution of 1 cc. Giemsa to 10 cc. of buffered distilled water.

(c) Wash in distilled water, blot, and dry.

2. *May-Grünwald-Giemsa Stain.* The staining with Giemsa stain as described above is often preceded, for a stronger and more lasting result,

by the fixing and staining action of the May-Grünwald stock solution. The combination of the two stains is often called the Pappenheim panoptic method.

The May-Grünwald stain is an alcoholic solution of methylene blue eosinate.

Technic: (a) Cover the dry unfixed thin smear for two minutes with 10 drops of the May-Grünwald stock solution (for fixing and staining).

(b) Add 10 drops of buffered distilled water for three additional minutes (for staining).

(c) Wash in distilled water.

(d) Turn the slides over Giemsa stain as previously described (15 to 30 minutes).

(e) Wash, blot, and dry.

3. *Wright Stain.* The stock solution is made of

Wright's stain powder	0.3	Gm.
Glycerin (pure)	3	cc.
Methyl alcohol (pure and absolute)	97	cc.

Grind the powder in a mortar, add the glycerin, mix and add the alcohol. Filter and let the filtrate stand a week at room temperature or two days at 37 C. in an incubator.

The worker in the field may safely use the following method of preparation of the Wright stain:

To a 0.5 per cent aqueous solution of sodium bicarbonate add pure methylene blue in the proportion of 1 Gm. of the dye to each 100 cc. of the solution. Heat the mixture in a steam sterilizer at 100 C. for one hour, counting the time after the sterilizer has become thoroughly heated. The mixture is to be contained in a flask, of such size that it forms a layer not more than 6 cm. deep. After heating, allow to cool, placing the flask in cold water. Filter to remove the precipitate. To each 100 cc. of the filtered mixture add 500 cc. of a 1 per cent aqueous solution of "yellowish-water soluble" eosin and mix thoroughly. Collect on a filter the abundant precipitate which immediately appears. When the precipitate is dry, dissolve it in methylic alcohol (chemically pure) 0.1 Gm. to 60 cc. In order to facilitate the solution, the precipitate is to be rubbed with alcohol in a porcelain mortar. This alcoholic solution of the precipitate is the staining fluid. It should be kept in a well stoppered bottle because of the volatility of the alcohol. If it becomes too concentrated by evaporation and thus stains too deeply, or forms a precipitate on the blood smear, the addition of a suitable quantity of methylic alcohol will quickly correct such faults.

Technic: (a) cover the dry unfixed smear for two minutes with 10 drops of Wright's stock solution.

(b) Add 10 drops of buffered distilled water for three to five additional minutes.

(c) Wash in buffered water, blot, and dry in air.

* * *

For routine hematologic examination it is sufficient to estimate the hemoglobin and to do a white cell and differential count, the latter on 200 cells (hemogram). While not commonly practiced, it would be desirable always to convert the relative numbers obtained for each cell category into absolute numbers calculated on the basis of the leukocytic count. One should almost always observe that leukopenias are, in fact, neutropenias and that the lymphocytosis is only relative and gives a normal absolute figure. The normal hemogram in man, with its normal limits of variation for each cell species, can be calculated in absolute number on the basis of 7,500 leukocytes. The leukocytic count and the hemogram show fluctuations varying sometimes considerably (from one to two) from one day to the next, or even from one hour to the other, in the peripheral blood. Venous blood is therefore to be preferred. The following table gives the normal variations in the human hemogram:

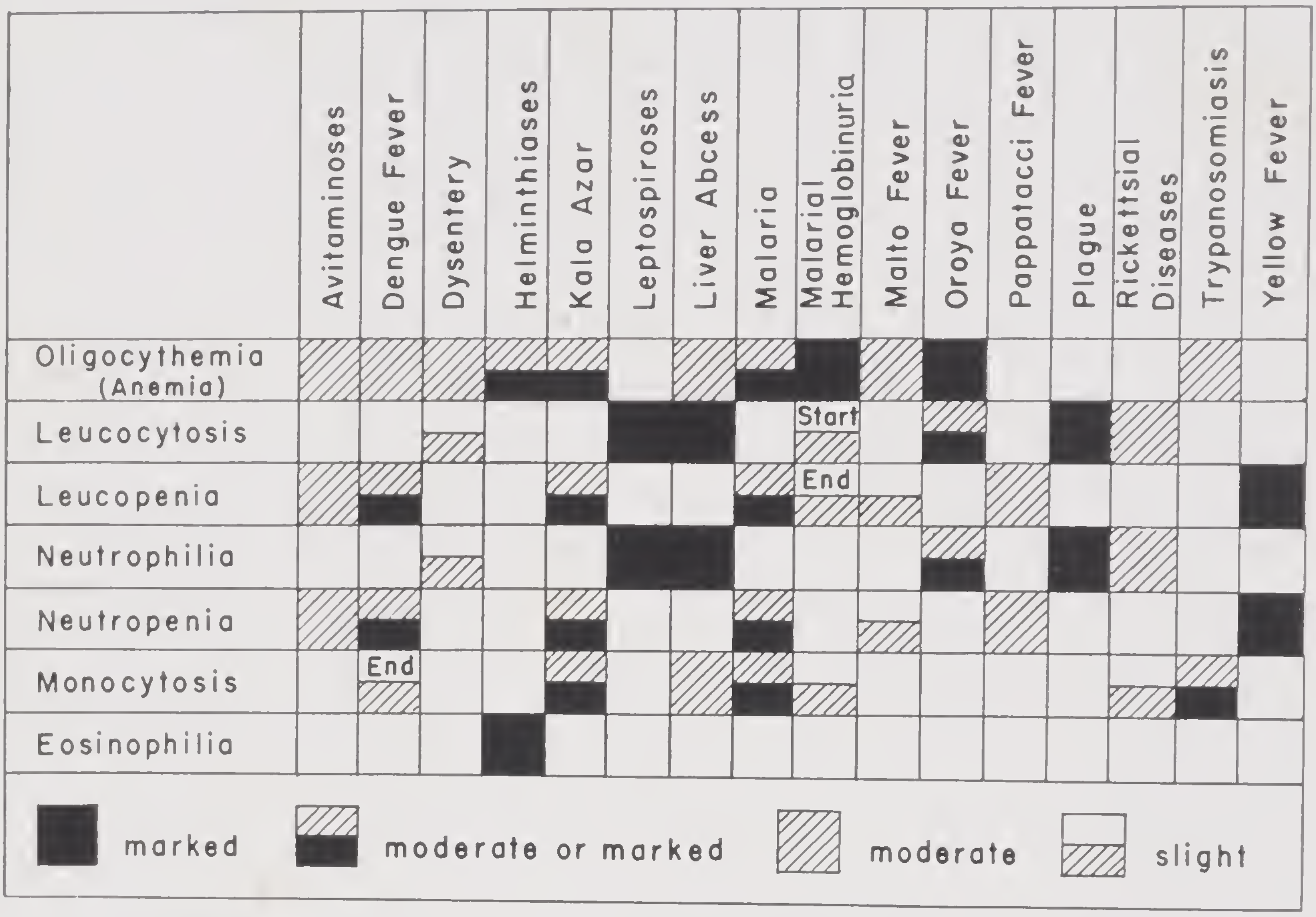
	Percentages	Absolute per cu. mm. on the basis of 7,500 leucocytes
Monocytes	2–8	150–600
Lymphocytes	21–35	1.575–2.355
Segmented neutrophilic granulocytes	50–70	3.750–5.250
Unsegmented neutrophilic granulocytes	0–6	0–450
Eosinophilic granulocytes	1–5	75–375
Basophilic granulocytes	0–1	0–75

The degree of pathologic variations encountered in diseases of the warm climates is shown in the accompanying table (page 421).

* * *

The easiest way to secure bone marrow is by puncture with a strong needle (1 to 1.5 mm. wide) of the sternum or the iliac crest. The latter method as advocated by van den Berghe is the most practical, especially among timid people and children.

The nuclear cell count is not so accurate for the bone marrow as for the blood, the former being always more or less diluted with blood from the marrow sinuses. One should, however, always practice a quantitative count of the bone marrow cells in order to interpret the picture of an otherwise very often obscure myelogram. In ten normal adults by puncture of the sternum or the ileum the average of the cellular count was: 70,000



	Avitaminoses	Dengue Fever	Dysentery	Helminthiases	Kala Azar	Leptospiroses	Liver Abcess	Malaria	Malarial Hemoglobinuria	Malta Fever	Oroya Fever	Pappatacci Fever	Plague	Rickettsial Diseases	Trypanosomiasis	Yellow Fever
Oligocythemia (Anemia)	▨	▨	▨	▨■	▨■		▨	▨■	■	▨	■				▨	
Leucocytosis			□▨			■	■		Start ▨		▨■		■	▨		
Leucopenia	▨	▨■			▨■			▨■	End ▨	□▨		▨				■
Neutrophilia			□▨			■	■				▨■		■	▨		
Neutropenia	▨	▨■			▨■			▨■		□▨		▨				■
Monocytosis		End ▨			▨■		▨	▨■	□▨					□▨	▨■	
Eosinophilia				■												

■ marked ▨■ moderate or marked ▨ moderate □▨ slight

Degree of Pathologic Variation Found in Tropical Diseases

± 12,447 (total) out of which 12,446 ± 2,542 were erythroblasts and 58,354 ± 9,579 leukocytes. Children between 1 and 10 years of age show a much higher count oscillating between 100,000 and 600,000.

Because of the very great number of cells present on a bone marrow smear, it is necessary to count 500 leukocytes, and separately the erythroblasts, the plasmocytes, the histocytes, and the macrophagic cells in percentage of these leukocytes. All the cells encountered, going from one edge to the other in the middle portion of the smear, should be counted. The figures given in the tabulated myelogram (page 422) represents an average of myelograms established on 50,000 cells from 10 normal bone marrows.

African natives show a very low count of mature granulocytes and a high count of young granulocytes. This may be related with malarial infections in the same way as neutropenia in the blood has been attributed to malaria.

The examination of bone marrow smears is especially useful for the discovery of *Leishmania donovani* parasites (kala-azar). For other tropical diseases, the value of the method has been insufficiently studied. Conflicting opinions have been reported for malaria and African sleeping sickness.

NORMAL MYELOGRAM OF MAN

(van den Berghe and Blitstein)

	Variations Limits	Mean
Procrythroblasts	0–0.5	0.22
Erythroblasts basophilic	0.2–1.7	1.00
Erythroblasts polychromatophilic	14.5–78	20.54
Erythroblasts orthochromatophilic	0–0.8	0.31
Total of erythroblastic cells	15.8–28.6	22.07
Myeloblasts	0.2–1.0	0.46
Premyelocytes	0–1.2	0.32
Myelocytes neutrophilic	8.4–16.8	12.27
Myelocytes eosinophilic	0.5–1.7	0.78
Myelocytes basophilic		Exceptional
Metamyelocytes neutrophilic	4.0–10.0	6.38
Metamyelocytes eosinophilic	0.2–1.6	0.65
Metamyelocytes basophilic		Exceptional
Granulocytes		
unsegmented		
neutrophilic	27.4–51.1	39.37
eosinophilic	0.4–2.6	1.25
segmented		
neutrophilic	3.2–12.8	8.73
eosinophilic	0.3–1.5	0.70
basophilic	0–0.2	0.09
Total of granulocytic cells		71.01
Total of eosinophilic cells		3.38
Total of basophilic cells		0.09
Lymphoblasts and Prelymphocytes	0.06–0.10	0.08
Lymphocytes	16.0–41.4	28.02
Premonocytes and Monocytes	0–2.7	0.97
Megakaryoblasts and Megakaryocytes	0–0.2	0.01
Plasmocytes	0.2–1.00	0.47
Histocytes	0–0.8	0.18
Macrophagic cells	0–0.2	0.02
Ratio, granulocytes/ erythroblasts	2.34–4.71	3.37

III. The Cerebrospinal Fluid

The first drops of fluid collected may contain some blood from the puncture and must therefore be used only for bacteriologic examination.

The total cell count is made with ordinary hemocytometer counting chambers (Fuchs-Rosenthal, Thoma, Neubauer, etc.).

In the African practice of sleeping sickness we use preferably the special chamber of Nageotte with which the number of the cells must be divided by 5 after the enumeration of 4 vertical rows (5 cu. mm.) and by 10 after the enumeration of 8 rows (10 cu. mm.).

The counts must be made immediately after the puncture as a lysis of the cells occurs very rapidly in the cerebrospinal fluid kept in vitro.

The special chemical examinations have been described in the section on diagnosis of African Trypanosomiasis.

IV. MICROSCOPIC STOOL AND URINE EXAMINATION

In the common practice of tropical regions, an examination of the feces is often limited to a search for parasites or ova.

The discovery of *Entamoeba histolytica* (vegetative forms and cysts) and of *Entamoeba coli* has been discussed at length in the section on Amebic Dysentery (see Chapter V). The cytologic diagnosis of the feces has also been given, comparing Amebic Dysentery with Bacillary Dysentery, in the section dealing with the latter (Chapter V).

Large helminths are found by macroscopic inspection of the stool. Larvae of flies are occasionally discovered in the feces.

Nearly all intestinal helminths deposit ova which are characteristic and easy to detect by microscopic examination. The ova of *Strongyloides stercoralis* generaly hatch in the intestine and appear as larvae in the feces. Ova of *Taenia saginata* ordinarily pass out while still within the segments of the worm, although some can be found in the feces after disintegration of segments.

One has to be familiarized with the microscopic appearance of the end products of digestion such as vegetable cells, starch granules, spores of fungi, muscle or fibrous tissue. Care must be taken not to take these structures for ova or cysts. These are more uniform in size and generally very characteristic of the species. Only the unfertilized, elongated and rather irregular eggs of *Ascaris lumbricoides* may be mistaken for a vegetable cell. As a rule when the structure seen is not typical in appearance and therefore doubtful, it is probably not an ovum or a cyst.

The yeastlike organisms *Blastocystis hominis* are sometimes very numerous, assuming many sizes and shapes and resembling more or less protozoal cysts. *Blastocystis hominis*, however, are easily recognized by their large central vacuole and the narrow surrounding rim of cytoplasm.

The following procedures are most valuable for the discovery and diagnosis of helminth eggs and protozoal cysts.

1. *Microscopic examination of feces.* A specimen of the stool, preferably of the outer part is diluted with physiologic salt and a drop examined between slide and cover slip. Similar preparations are made with the material removed by a perianal swab (best method for *Enterobius* eggs) by anal or rectal swab (best method for *Schistosoma mansoni* eggs) and with the sediment of centrifuged urine (*Schistosoma haematobium*) or the sputum (*Paragonimus westermani*).

2. *Willis flotation technic.* Approximately one part of feces is mixed with ten parts of a saturated solution of table salt. After ten minutes many eggs and most protozoal cysts float to the surface. The technic is performed in glass tubes approximately 5 cm. high by 1.5 cm. wide filled to the rim. The harvest of eggs and cysts is obtained on superimposed clean square cover slips. The method is very useful for cysts of *Entamoeba histolytica.* It is not satisfactory for the heavy eggs of *Schistosoma mansoni* and *Clonorchis sinensis.*

3. *Zinc sulfate centrifugal flotation technic* (Faust and associates, 1938, 1939). One part of feces is mixed with ten parts of lukewarm tap water. Ten cc. of the suspension are strained through wet cheesecloth (small funnel) into a tube which is centrifuged for sixty seconds at 2,500 r.p.m. The supernatant fluid is poured off and the sediment is broken up with water and by shaking, then centrifuged with additional water. This is repeated until the supernatant fluid is clear. The fluid is finally replaced in the same way by 33 per cent zinc sulfate solution (specific gravity 1,180) and the tube centrifuged for sixty seconds at 2,500 r.p.m. The floating material on the surface of the tube is removed with a bacteriologic loop, mixed with a drop of iodine solution and examined on a slide under a cover glass.

A simplified method has been introduced by Otto, Hewitt, and Strahan (1941) whereby the 33 per cent zinc sulfate solution is used directly as a flotation medium without straining the feces through cheesecloth. The protozoan cysts and helminth eggs floating on top of the tubes are obtained on superimposed cover slides. This modification of the original technic of Faust and associates is slightly inferior to protozoan cysts and better for helminth eggs.

4. *Centrifugation.* The following method has been found very satisfactory both for protozoan cysts and helminth eggs at the Tropical Institute in Antwerp. Feces are mixed with formol saline 10 per cent. The suspension is strained through a silk cloth which has 30 holes per cm., the holes averaging 250 μ in diameter. The preparation is then centrifuged for one minute at 2,000 r.p.m. The supernatant fluid is poured off and the packed sediment broken off with the following medium (density 1.047, after Carles and Barthelemy):

Citric acid	12 Gm.
Water	86 Gm.
Formol 40 per cent	2 Gm.

Two cc. of ether is added, the mixture is shaken thoroughly and centrifuged for 30 seconds at 2,000 r.p.m. The separation zone between the ether and the fluid is then stirred with a pipet to liberate some of the cysts which might float on the surface of the fluid and the tube is centrifuged again for 30 seconds at 2,000 r.p.m. The supernatant fluid is poured off and the sediment examined under the microscope, after some iodine solution has been added.

5. *Stoll technic.* This method has been especially used to estimate the number of eggs of Ancylostoma or Necator in a weighed sample of feces. Four Gm. of feces are weighed and diluted to the 60-cc. mark of a graduated flask with decinormal sodium hydroxide. Glass beads are added and the flask closed and thoroughly shaken until an even suspension is obtained; 0.15 cc. of the suspension is drawn with a graduated pipet and examined under a 22 by 40 mm. cover glass. The total number of eggs of the particular species is counted and multiplied by 100 to obtain the number of eggs per Gm. of feces. An estimated daily output of eggs (depending, however, on the consistency of the feces) can then be calculated by multiplying the number per Gm. by the total weight of the twenty-four hour stools.

V. Research of Fungi

Pus or sputum is examined unstained in thin smears between slide and cover glass. If necessary the preparation may be cleared by adding a drop of 20 per cent potassium hydroxide and warming the slide gently.

Scrapings of ulcers, skin lesions, and hairs are examined in 20 per cent potassium hydroxide. Nail scrapings require more time for clearing.

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